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STUDIES ON HYPERSENSITIVITY*

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THE FIRST HALF of the present century has witnessed a phenomenal progress in the understanding, diagnosis, treatment and prevention of disease. While many of the medical achievements of this half-century have been built in logical progression upon foundations laid by the remarkable men of genius who flourished in the last century, many others are, as far as that is ever possible in science, new developments of a new era. One of the highly important and extremely interesting achievements of the latter class is the development of concepts and of knowledge relating to hypersensitivity. Before the present century, the word "allergy" did not exist. The phenomenon of bacterial hypersensitivity had been discovered by Koch at the end of the last century, but it was not until the present century that Richet and Portier discovered and named anaphylaxis; that Arthus discovered the phenomenon that bears his name; that serum sickness was first described, studied and named by von Pirquet and Schick; that the relation of antibody to hypersensitivity was first indicated by Hamburger and Moro; and that the phenomenon of desensitization was clearly exposed by Besredka. And it was not until the present century that it was recognized that hypersensitivity can produce serious disturbances of the respiratory tract and the alimentary tract; of the cardiovascular, the urinary, the hæmatopoietic, the ocular, and the nervous systems; that it damages the connective tissues and the joints, and is responsible for a multiplicity of cutaneous disorders; nor was there any suspicion that a vast number of different environmental substances, which are in themselves relatively harmless, can produce distressing and even fatal disease through their capacity to induce the hypersensitive state.

This discussion will be confined to a review of some aspects of hypersensitivity which my associates and I have studied, and with which, therefore, I have more immediate familiarity; though in so doing, I am keenly aware that I shall hardly be touching the surface of this vast and important field.

One can roughly separate the disorders produced by hypersensitivity into two categories. First, there are the primary diseases of hypersensitivity, i.e., those in which the disease state is the result of hypersensitivity to agents that are not, in themselves, intrinsically harmful on usual contact, and in which, had hypersensitivity not developed, no significant lesions or symptoms attributable to the agent would have occurred. In this category belong, of course, the hypersensitive reactions of pollens, dusts, foodstuffs, drugs, and industrial chemicals; and the effects belong to the general group of anaphylactic reactions.

The second category comprises the diseases that are accompanied by sensitization, i.e., those conditions in which disease is produced by agents which are themselves injurious, but in which the disease process becomes intensified by the sensitization that develops as a result of contact with the agent. Such agents are, particularly, microörganisms, viruses and animal parasites.

While the anaphylactic type of sensitivity occurs not infrequently as a result of parasitic infestation, and may also result from sensitization to some of the products of bacteria and fungi, particularly carbohydrate products, the more characteristic form of sensitization produced by infection with microörganisms is sensitization to the proteins of the agent, and it differs in a number of ways from the anaphylactic type of sensitivity. This hypersensitivity of infection is commonly referred to as "tuberculin-type" sensitivity, for its prototype is the hypersensitivity to tuberculoprotein that develops during tuberculous infection. As is well known, the local inflammatory response to the antigen in this type of hypersensitivity is delayed and prolonged, in contrast to the explosive and evanescent character of the anaphylactic urticarial wheal; in contrast to the ease of passive transfer of the anaphylactic type of sensitivity by injecting the serum of the sensitized body into a normal one, passive transfer of tuberculin-type sensitivity cannot be accomplished by serum; the smooth muscle of the anaphylactically sensitized body is thrown into spasmodic contraction on contact with the antigen, but this does not occur in the case of tuberculin-type sensitivity; and finally, as we were able to show some years ago,[1] washed cells of the body with tuberculin-type sensitivity are killed *in vitro* by contact with the antigen, whereas those of the anaphylactically sensitized body are unharmed by such contact.[2]

The role played by tuberculin-type hypersensitivity, especially in chronic infections, is an impor-

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tant one, for it can enormously intensify tissue damage and destruction and the debilitating systemic effects that a given amount of the infecting agent is capable of producing. It was believed for many years that the intensified inflammation that results from the hypersensitive damage to tissues was an essential mechanism of acquired immunity in tuberculosis and certain other infections, and that the increased destruction of tissue resulting from this type of hypersensitivity was a necessary evil that had to be accepted in order to obtain the benefit of the exaggerated inflammation. Experimental studies in our laboratory, extending over a period of years, demonstrated in a variety of different ways, and in a variety of different acute and chronic infections, including tuberculosis and syphilis, that the exaggerated inflammation of hypersensitivity is not at all necessary for the operation of acquired immunity.[3] I shall illustrate only one of the several methods that were used to dissociate immunity from hypersensitivity, namely, desensitization.

These studies, which demonstrated that immunity remains completely intact when local and systemic hypersensitivity is abolished by desensitization, have been confirmed by many investigators;[3] and Raffel[4] subsequently dissociated hypersensitivity from immunity by a different attack, showing that it is possible to establish a high degree of tuberculin-type hypersensitivity to the tubercle bacillus without any concomitant development of resistance to the infection whatever. These various studies have served to free us from the fatalistic doctrine that hypersensitive tissue damage, when it occurs during infection, is a sacrifice that has to be endured in order to obtain protection against the invading microörganisms. It is now clear that the tuberculin type of hypersensitivity cannot in itself protect, and that it is no more necessary for protection against infectious agents than is the anaphylactic type necessary for protection against the antigens of the allergic diseases such as asthma and hay fever. In both types of hypersensitivity, the prevention of the hypersensitive reaction by desensitization can spare the body from unnecessary damage. There is a pressing need for the development of a safer and more efficient method of desensitization than we now possess.

The number of sensitizing agents responsible for the first category of disorders of hypersensitivity that I mentioned, i.e., agents which in themselves do not ordinarily injure the body unless hypersensitivity develops, is very large, for it includes not only naturally occurring substances such as pollens and foodstuffs, but also many industrial chemicals that are incorporated into a great variety of articles in our everyday environment, and in addition, a large and rapidly multiplying number of drugs used in the treatment of disease. The number of manufactured sensitizing substances to which the population is exposed is therefore continually increasing, and at a continually accelerated rate. If it is true that civilization has made great advances in the treatment and prevention of disease, it is no less true that in many directions it has created conditions favourable for the development of disease, and agents capable of producing disease. This is notably true in the case of the diseases of hypersensitivity. The number of sensitizing substances to which primitive man was exposed was relatively small, being limited to the naturally occurring products of the plants and animals in his immediate environment. Civilized man, through intensive adaptation and domestication, has greatly multiplied the variety of sensitizing plants and animals in his environment, and has, in addition, introduced into his environment a multitude of synthetic sensitizing agents.

While the complete spectrum of the injurious effects of hypersensitivity has doubtless not even yet been brought in view, our knowledge regarding the types of damage that can result from sensitization was greatly enlarged by the introduction of the sensitizing sulfonamide drugs. It was recognized in the early part of the century that proteins foreign to the body are active sensitizing antigens, and that phenomena of hypersensitivity result from the interaction of the antigen with antibody produced in response to the presence of the foreign protein antigen. The brilliant work of Landsteiner[5] then demonstrated that even a non-protein substance can induce highly specific hypersensitivity if it possesses a chemical constitution that permits it to attach itself to a normal protein of the body, thus forming, in effect, a new, "foreign" protein which stimulates the production of an antibody specific for the chemical substance that attached itself to the protein. Following the introduction of the sulfonamides it was shown by several investigators[6] that these and other sensitizing drugs can, under favourable conditions, attach themselves to plasma protein, and thus fulfil the basic requirement for the conversion of a non-protein chemical substance into a sensitizing antigen.

The sudden and extremely widespread use of the sensitizing sulfonamide drugs, which produce in many persons protracted hypersensitive reactions, soon provided an unprecedented opportunity to study the tissues of many patients who had developed such hypersensitive reactions shortly before death, and the striking findings restimulated interest in the pathological and experimental investigation of the tissue effects of generalized hypersensitive reactions of the protracted anaphylactic type. The results of those studies have made it unmistakably clear that a remarkable variety of inflammatory and necrotizing lesions of hitherto uncertain pathogenesis can result from protracted anaphylactic reactions to drugs and to foreign proteins.

Shortly after the introduction of the sulfonamides, for example, we began to encounter in our autopsy service an association of periarteritis nodosa and sulfonamide hypersensitivity with a fre-

quency that seemed to us far too great to be attributed to mere coincidence.[7] Pursuing these observations experimentally, Dr. Gregory and I[8] were able to demonstrate that this destructive and commonly fatal vascular lesion can be produced in animals by subjecting them to a protracted hypersensitivity reaction of the anaphylactic type, induced by non-toxic foreign proteins.

The experimental production of periarteritis nodosa by hypersensitivity has been confirmed by many investigators. We have also reported the occurrence of periarteritis nodosa in a patient during a hypersensitivity reaction to foreign serum;[7] in another, who died from a severe hypersensitive reaction to iodine;[9] and in another, who had exhibited hypersensitivity to aspirin.[10] Others have since reported the development of periarteritis nodosa during hypersensitive reactions to a wide variety of other drugs, including Dilantin,[11] thiourea,[12] phenobarbital,[13] arsenicals,[14] and antibiotics. It is now thoroughly established that periarteritis nodosa is one of the serious, injurious effects that the antigen-antibody reaction responsible for the anaphylactic type of hypersensitivity can produce.

Selye[15] has observed that periarteritis nodosa develops in rats kept on a high sodium diet and given large amounts of desoxycorticosterone. Since the administration of sodium and desoxycorticosterone produces hypertension in the rat, it is important to state that subsequent studies by numerous investigators have shown that in the rat, hypertension, no matter how produced, leads to the development of precisely the same periarteritis nodosa-like vascular lesions. Now treatment with sodium and desoxycorticosterone produces periarteritis nodosa-like lesions only in the rat, and the other methods of producing hypertension likewise fail to cause inflammatory vascular lesions of this type in animals other than the rat. The rat is peculiar in its vascular reaction to hypertension. I may say that periarteritis nodosa caused by hypersensitivity can occur in man, and can be produced experimentally in animals, in the complete absence of hypertension.

Zeek, Blankenhorn, and their associates[16] have sought to differentiate their human cases of periarteritis nodosa that were clearly due to hypersensitivity from those in which no sensitization was apparent, and which they term "primary" periarteritis nodosa. I think I should say that our own experience, as well as that of others, does not support the validity of the criteria which these authors advance as evidence for the existence of non-hypersensitive periarteritis nodosa distinguishable pathologically from periarteritis nodosa due to hypersensitivity. We have been able to produce experimentally, by means of hypersensitivity, all of the pathological criteria which they regard as specific for what they term "primary", non-hypersensitive periarteritis nodosa. Also, all of the clinical manifestations which they list as distinguishing criteria can occur in periarteritis nodosa definitely caused by hypersensitivity. I should, however, like to stress emphatically that it would be altogether improper to insist that periarteritis nodosa-like lesions in man can be caused only by hypersensitivity. There is evidence that under certain conditions necrotizing-inflammatory arteritis may result from sudden local alterations in circulatory dynamics, independently of hypersensitivity. This is particularly suggested by the occasional occurrence of focal necrotizing-inflammatory vascular lesions in the pulmonary arterial tree in cases of pulmonary arteriolar emboli, and also by the necrotizing-inflammatory arteritis of the mesenteric arteries that occurs in some cases following the abrupt circulatory alterations produced by the surgical repair of a coarctation of the aorta. Whether in cases such as these the vascular lesion results from the sudden alteration in pressure, or from ischæmia produced by spasm, or from some other cause, is not clear at present.

Certainly, in every case of periarteritis nodosa, the etiology should be carefully sought for, and with a completely open mind. However, it is now firmly established that this life-threatening vascular lesion can be caused by hypersensitivity to a wide variety of substances ranging from complex proteins to simple elements such as iodine; and since, from experience with human periarteritis nodosa caused by drug hypersensitivity, and also from experimental studies, we now know that cessation of contact with the sensitizing antigen ends the progress of the disease, it is of no little importance to search meticulously for an offending antigen in each case in which the cause is obscure.

In addition to this destructive vascular lesion, the abundant material provided by cases of sulfonamide hypersensitivity, followed by clinical, pathological and experimental studies of hypersensitivity to other sensitizing drugs and to foreign protein, has firmly established that an extraordinary variety of other visceral lesions can result from hypersensitivity. These lesions include a peculiar type of pneumonic consolidation, myocarditis, endocarditis, focal collagen degeneration, focal necrosis of lymph nodes and spleen, the formation of tuberculoid granulomata in the viscera, purpura, agranulocytosis, hæmolytic anæmia, neuritis, enteritis, arthritis, and glomerulonephritis. The information that the lesions mentioned can result from hypersensitivity, and that many drugs possess the sensitizing potentiality to produce them, is of major consequence. In the first place, it has become clear that unless a patient receiving a sensitizing drug is carefully watched for the occurrence of a hypersensitive reaction, and the administration of the drug promptly stopped if a reaction appears, he may suffer irreparable damage, or may even die, from the hypersensitivity effects of the drug administered to benefit him. Indeed, I have recently observed the case of a distinguished physician who took penicillin for an attack of sinusitis and de-

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veloped a severe hypersensitive reaction of the serum sickness type. In spite of that, he repeatedly took penicillin whenever his sinusitis recurred, even though each time that he took it he developed a hypersensitive reaction with urticaria. After a number of these episodes his blood pressure, which had always been normal, began to rise, and he developed a rapidly progressive malignant hypertension, from the effects of which he died within several months. At autopsy, we found periarteritis nodosa, which had involved and markedly narrowed the intrarenal arteries. This had greatly reduced the blood supply to the kidneys, and had produced hypertension from renal ischæmia.

In the second place, when faced clinically with one of the above-mentioned disease states in the absence of any other recognized etiological agent, it is of some importance to keep in mind the sensitizing potentialities of numerous drugs in common use by the laity and to which little attention is ordinarily paid, such as aspirin, a variety of sedatives, and the phenolphthalein laxatives, all of which have the capacity to produce sensitization.

The problem of drug hypersensitivity has become so serious as a result of the introduction of a continuously increasing number of new, sensitizing useful drugs, that an international symposium devoted exclusively to the problem of drug sensitivity is being held this summer in Liège.*

While it is, of course, thoroughly well recognized by the medical profession at large that asthma, hay fever, gastro-intestinal disturbances and a variety of cutaneous lesions can be caused by hypersensitivity, it is of no less importance to be aware of the fact that the other types of serious and even life-threatening lesions that I have mentioned can also result from hypersensitivity. This is not yet sufficiently widely appreciated. There can be little doubt that numerous patients who suffer from lesions of this class fail to receive the advantage of a proper search for an offending antigen because of the lack of appreciation of the fact that hypersensitivity is one of the causes of the condition in question.

I should like to discuss very briefly several of the visceral lesions now definitely known to be producible by hypersensitivity. The view that *pneumonitis* may result from hypersensitivity was brought into focus by the clinical studies of Harkavy[17] and others, who have established that relationship by demonstrating the close association of transient pulmonary infiltrations with asthma, urticaria, angioneurotic œdema, and other allergic conditions. Dr. Gregory and I[18] have described the peculiar pathological features of this allergic pneumonitis occurring in patients during hypersensitive reactions to drugs. It is characterized by damage to the alveolar capillaries, leading to exudation of fluid, the formation of hyaline alveolar membranes, focal exudation of leukocytes and, when the damage is more severe, to thrombosis of capillaries or to rupture, with hæmorrhage into alveoli. Lesions of this type are simply the pulmonary analogues of cutaneous anaphylactic urticaria, angioneurotic œdema and purpura. Pulmonary lesions of precisely the same type occur in periarteritis nodosa, and, interestingly from the standpoint of pathogenesis, in rheumatic fever and disseminated lupus erythematosus.

It is now clearly established that *myocarditis* can result from hypersensitivity. The exceptional opportunity provided by the sulfonamides to study the tissues of patients who died during hypersensitive reactions to these drugs soon led to the recognition by French and Weller,[19] ourselves[7] and others that hypersensitivity can produce focal inflammatory infiltration of the myocardium, the inflammatory cells being predominantly mononuclears, accompanied by eosinophils and neutrophils. In areas of intense inflammation, cardiac muscle fibres may become necrotic. The same type of myocarditis has been observed in cases of human anaphylactic serum sickness by Clark and Kaplan[20] and by ourselves.[7] We have reported its occurrence in a fatal hypersensitive reaction to iodine,[9] and have observed it in patients who have died during hypersensitive reactions to other drugs, including streptomycin and penicillin, and in severe allergic asthma complicated by Loeffler's eosinophilic pneumonitis.

It is obvious that cardiac damage of this character, occurring during therapy with sensitizing drugs, can, when extensive, be a decided hazard to life.

It is of considerable interest and importance that the anaphylactic type of hypersensitive reaction to soluble antigens is capable of producing not only the banal types of inflammatory lesions, but also lesions of a distinctly *tuberculoid* character, i.e., accumulations of epithelioid cells and giant cells, which closely simulate tuberculous lesions. We have reported the development of lesions of this type in patients who died from hypersensitive reactions to sulfonamides, to iodine, and to Dilantin, and in fatal asthma with eosinophilic pneumonitis, and the literature contains similar observations. Doubt that these tuberculoid lesions in man are really a result of hypersensitivity has been removed by the experimental production of the lesions by subjecting animals to protracted hypersensitive reactions resulting from the intravenous injections of bland foreign protein,[21] an observation that has been confirmed by others.

Why only some of the individuals exposed to a given antigen develop lesions of this type, and why, in the same body, some of the lesions of hypersensitivity may assume this tuberculoid character while others are of the more usual inflammatory type, are matters which invite especial study for the light that may be thrown upon the still obscure subject of the pathogenesis of tubercle formation in tuberculosis and in other infections in which a

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tuberculoid reaction occurs, including syphilis, brucellosis, tularæmia, blastomycosis, lymphogranuloma venereum and sarcoid.

It is of particular interest to discuss briefly the relation of the anaphylactic type of hypersensitivity to *glomerulonephritis*, a relationship which has long been suspected. Particularly suggestive in this regard has always been scarlatinal nephritis and the nephritis that is associated with tonsillitis, in neither of which, as is well known, does the nephritis appear during the height of the infection when the streptococci and their products are present in greatest abundance, but only after a lapse of time sufficient to permit an active development of antibody and of hypersensitivity. In the early part of the century, Schick[22] and others compared this delay in the appearance of scarlatinal nephritis to the situation in serum sickness, in which the presence of the foreign serum in the circulation provokes no symptoms until a sufficient amount of sensitizing antibody has been produced.

In 1913, Longcope[23] reported that he had observed lesions, similar to those in human glomerulonephritis, in animals subjected to repeated injections of foreign protein, and during the succeeding 45 years one or two other investigators mentioned similar observations. Doubt was always cast upon these reports, because the illustrations did not provide acceptable evidence that lesions typical of those of human glomerulonephritis had been produced. In our experimental studies on periarteritis nodosa, Dr. Gregory and I[8] reported the production of glomerulonephritis in rabbits subjected to a protracted hypersensitive reaction under conditions which permit a circulating antigen to interact with the antibody that is produced as a response to its presence. This can be accomplished most simply by introducing into the circulation a bland foreign protein, such as horse serum or egg albumen, in an amount that will permit some of it to remain in the circulation until antibody and hypersensitivity make their appearance. We found that under these conditions a considerable percentage of the animals develop acute glomerulonephritis. This has been confirmed by many investigators who have repeated this experimental procedure. The lesions, which may be focal, involving only a portion of the tuft of some of the glomeruli as in many cases of human periarteritis nodosa, or may be diffuse, reproducing the characteristics of ordinary human acute proliferative glomerulonephritis, have recently been illustrated in detail, together with a discussion of the significance of this nephritis of hypersensitivity in relation to the pathogenesis of acute glomerulonephritis in man.[25] Dr. John Hamilton, Dr. Chester McLean and their co-workers[24] have produced glomerulonephritis, proceeding to uræmia, by introducing small amounts of protein repeatedly into the circulation of animals sensitized to it.

While there was every reason to believe that this experimental glomerulonephritis was a result of hypersensitivity, the immunological studies of Janeway and his co-workers[26] and of Germuth[27] on the correlation between the antigen-antibody relationships and the development of the glomerular lesions, served to place on a much stronger foundation the role of hypersensitivity as the cause of the experimental nephritis. The crucial test of whether a given effect is actually a result of an antigen-antibody reaction depends, however, upon the production of the effect by passive transfer, i.e., by introducing the antigen, and the antibody from a sensitized animal, into a previously normal animal. Dr. John Hamilton[28] has succeeded in accomplishing this, and Dr. Germuth, in our laboratory, has recently confirmed his results. Dr. Germuth[29] has found that surprisingly well-marked glomerular lesions of acute proliferative glomerulonephritis can make their appearance within 48 hours of the introduction of antibody into the blood stream of a normal animal if antigen is introduced very slowly by continuous intravascular infusion during that period.

The experimental glomerular lesions, together with the immunological evidence, demonstrate clearly the important fact that glomerular lesions characteristic of ordinary human glomerulonephritis, and which can lead to uræmia in the experimental animal, can result from a pure hypersensitive reaction produced by antigens possessing no primary toxicity. It will be remembered that in human serum sickness resulting from hypersensitivity to therapeutically administered foreign serum there commonly occur, though usually in only moderate degree, disturbances of renal function of the type encountered in glomerulonephritis. That acute nephritis in man can result from hypersensitivity to non-toxic, non-bacterial antigens is also indicated by cases such as those described by Longcope and Rackemann[30] and by Ehrström,[31] in which an attack with the clinical and renal functional characteristics of acute nephritis would promptly occur whenever a foodstuff to which the person had become sensitized was ingested.

We have observed, in common with other investigators, that in the experimental nephritis produced by hypersensitivity, albuminuria and hæmaturia appear only after a latent period sufficient to permit the development of hypersensitivity. In this, the experiments provide support for regarding the well-known latent period between the height of a streptococcal infection and the appearance of acute nephritis in man as being the period during which sensitizing antibody is being formed. The close relationship of the hæmolytic streptococcus to many cases of human acute glomerulonephritis, and the important demonstration by Rammelkamp[32] that different types of Group A streptococci differ markedly in their tendency to cause glomerulonephritis, warrants a pointed study of the sensitizing substances of these bacteria in relation to their ability to cause glomerulonephritis.

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Because of the wide variety of lesions which rheumatic fever and rheumatoid arthritis exhibit in common with protracted anaphylactic reactions, shortly after Hench and his co-workers reported the spectacular effect that cortisone and ACTH exert upon rheumatic fever and rheumatoid arthritis Dr. Berthrong, Dr. Bennett and I[33] sought to determine whether the production of the experimental cardiovascular and renal lesions of hypersensitivity would be suppressed by those hormones. This was found to be the case. In relation to experimental anaphylactic glomerulonephritis, we found that ACTH or cortisone exerted a markedly protective effect, maintaining the glomeruli in a perfectly normal state in the great majority of the sensitized animals; and this has been confirmed by others.

No significant success has attended the treatment of human acute glomerulonephritis with these hormones. I would emphasize that in our experiments the hormones were administered from the very beginning of the period of sensitization. They represent, therefore, experiments dealing with the *prevention* of the damage. There is good reason to believe that by the time that oliguria, macroscopic hæmaturia, œdema or symptoms have appeared in human acute glomerulonephritis, the greater part of the damage in most cases has been completed, and it may already be too late to affect the course of the nephritis appreciably. However, in view of the suppressive effect of these hormones upon the experimental nephritis, and upon antibody formation and inflammatory reactions in general, it would seem worthwhile to continue to study their effect upon the development of human acute nephritis in appropriate cases, particularly in the attempt to institute treatment at the earliest possible moment at which urinary abnormalities can be detected by frequent examinations of the urine following streptococcal infection, in order to prevent any further glomerular damage if the process is still in evolution.

Time permits only a cursory mention of a highly important group of serious diseases, in most of which the role of hypersensitivity has not yet been conclusively demonstrated, but which exhibit in common a wide variety of clinical and pathological manifestations that are known to be effects which the anaphylactic type of hypersensitivity is capable of producing. These are the "collagen-vascular diseases", so called because they are characterized by widespread focal degeneration of collagen fibres, and by endothelial and vascular injury. This group includes, particularly, rheumatic fever, rheumatoid arthritis, disseminated lupus erythematosus and periarteritis nodosa. Some instances of dermatomyositis and scleroderma exhibit similar collagen and vascular injury. It is now clearly established, as we have seen, that one of these diseases, periarteritis nodosa, can be caused by anaphylactic hypersensitivity. All of them exhibit clinical and pathological phenomena which anaphylactic hypersensitivity is known to produce, namely, fever, arthritis, cutaneous eruptions, purpura, myocarditis, sterile pleuritis or pericarditis, anaphylactic type pneumonitis, necrosis and inflammation of arteries, focal collagen degeneration, and other lesions. The studies of Coburn,[34] Klinge[35] and others long ago strongly suggested that hypersensitivity plays an important role in the pathogenesis of rheumatic fever. My associates and I, in studies that have been confirmed by numerous investigators, have demonstrated the similarity of the basic characteristics of the cardiac, pulmonary and vascular lesions of the collagen-vascular diseases to those that occur in protracted anaphylactic reactions in man and in the experimental animal. These similarities we have abundantly illustrated elsewhere.[10, 36]

Identity of lesions is, of course, no absolute proof of identity of etiology or pathogenesis; and until further study defines precisely the cause of each of the collagen-vascular diseases, we can say only that the evidence for the role of an antigen-antibody reaction in the pathogenesis of the lesions of rheumatic fever, rheumatoid arthritis, and disseminated lupus is highly suggestive; though it may certainly be that some other, as yet undiscovered, process will be shown to produce the same extraordinary multiplicity of effects as those known to be caused by hypersensitivity. The numerous recent observations that the drug hydralazine can produce clinical and laboratory characteristics of disseminated lupus erythematosus, even to the point of bringing into existence the serum factor responsible for the formation of the L.E. cell, is of the highest interest.

The recent work of Vazquez and Dixon[37] is suggestive in relation to the problem of whether an antibody reaction is concerned in the pathogenesis of the collagen-vascular diseases. It is well known that antibodies are found largely in the gamma globulin fraction of the serum. Using the fluorescent antibody technique, Vazquez and Dixon found that normal tissues and ordinary acute inflammatory lesions contain more albumin than globulin, whereas in the lesions of rheumatic fever, rheumatoid arthritis and disseminated lupus erythematosus there is a concentration of globulin and little albumin. The suggestion that the globulin concentrated in the lesions of these collagen-vascular diseases may be antibody globulin is obvious, but definite interpretation must wait upon a more precise identification of the nature of the globulin.

In relation to the possible role of an antibody-antigen reaction in the pathogenesis of the collagen-vascular diseases, it is of interest that patients with agammaglobulinæmia are markedly susceptible to infections, but no valid case of a collagen-vascular disease has yet been observed in these individuals who lack the ability to produce antibodies.

In the consideration of the possible role of an antibody-antigen reaction in the pathogenesis of these diseases, it is of some importance to bear

in mind that not all antibodies are directed against exogenous antigens. The existence of autoantibodies directed against the body's own tissue substances, is a phenomenon of rapidly growing prominence, particularly in the domain of hæmatological disorders.

The precise nature of the collagen alteration in the lesions of the collagen-vascular diseases is not yet well understood. In the lesions of all these diseases the collagen fibres undergo swelling, hyalinization, fragmentation and disintegration into a formless débris. Now it has been known for 50 years that precisely these alterations of collagen fibres occur in the Arthus reaction, which is the local lesion produced by the injection of the specific antigen into the tissues of the highly sensitized anaphylactic body. Some years ago, Schmitt and his associates[38] found that each normal collagen fibre, which appears homogeneous under the ordinary light microscope, is really composed of bundles of minute, cross-striated fibrils visible only with the electron microscope. Dr. Voisin, Dr. Bang, and I[39] have sought to learn what happens to the structure of these electron microscopic fibrils in anaphylactic lesions, and we found that they lose their periodic cross-striations and undergo degenerative alterations strikingly like those characteristic of the gross fibres visible with the ordinary microscope both in anaphylactic lesions and in the lesions of the collagen-vascular diseases. It would appear that the alterations of the fibres visible with the ordinary microscope represent merely a summation of the alterations in their component electron microscopically visible fibrils.

Unfortunately, the mechanism through which the antigen-antibody reaction of hypersensitivity produces this marked alteration of the ultramicroscopic structure of collagen, or produces the inflammatory and vascular lesions that characterize anaphylactic hypersensitive tissue damage, is still completely obscure. It is perfectly clear that the interaction of antibody and antigen in the tissues can produce serious tissue damage, and there is good reason to believe that complement is implicated in the process; but how the antibody-antigen interaction produces the injury eludes us. This is a problem of urgent importance in all of the manifold types of injury produced by hypersensitivity. Histamine can, as is well known, produce certain effects that anaphylactic reactions produce. Because of this and of other suggestive observations, it has been tempting to believe that anaphylactic phenomena may be results of the action of histamine, liberated in some way as a consequence of the antibody-antigen interaction. Perhaps some of the anaphylactic phenomena can be so explained. However, Croxatto,[40] in our laboratory, was unable to produce anything resembling the violently inflammatory, hæmorrhagic and necrotizing anaphylactic Arthus reaction, regardless of the amount of histamine injected into the tissues; nor did histamine produce the alteration of collagen that is so striking an effect of many anaphylactic reactions, and which I have just described. Furthermore, it was shown by Bloom,[41] in our laboratory, that histamine has virtually no power of evoking a cellular inflammatory exudate, whereas an abundant cellular exudate, often rich in eosinophils, is a common occurrence in tissue hypersensitivity reactions. There is, of course, no necessity for assuming that all observed effects of antibody-antigen interaction are produced by a single mechanism.

If we began this discussion by commenting upon the remarkable advance in knowledge relating to hypersensitivity during the past 50 years, we must end it by stressing the increase in the area of our ignorance which that advance has revealed. It is one of the paradoxes of science that each new extension of the realm of the known, instead of decreasing the area of the unknown, increases it; for the answer to each question holds in itself the germs of a swarm of new questions. In conformity with this, the marked progress in knowledge relating to hypersensitivity since the beginning of this century has generated innumerable new and unsolved problems, many of them of fundamental importance. Why do only some, and not all persons who are equally exposed to a sensitizing agent become sensitized, and why does contact with the antigen produce injurious effects in some but not in all of those who become sensitized? Why is one tissue attacked in some who are sensitized to a given substance, and a different tissue in others who are sensitized and exposed in the same manner to the same substance? What are the conditions under which antigen will interact with antibody to produce injurious effects, and, most important in its therapeutic implications, what is the mechanism through which the tissue injury is produced? What is the basic meaning of this remarkable process through which the body so alters itself that nontoxic substances become able to produce highly injurious effects? These and many other fundamental problems remain to be solved before we shall be able adequately to understand the phenomenon of hypersensitivity; and their solution cannot fail to have important practical effects upon the prevention and treatment of the manifold allergic disorders that plague mankind.

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RÉSUMÉ

Le mot allergie date du xx^e siècle de même que les principales découvertes dans ce domaine à compter de Richet, Arthus, von Pirquet, Schick, etc. Les troubles de l'hypersensibilité se divisent en deux grandes catégories. Il y a d'abord ceux qui résultent de l'activité d'agents qui ne sont pas eux-mêmes intrinsèquement nocifs et qui, sans la présence de cette hypersensibilité seraient anodins. A ce groupe appartiennent les pollens, les poussières, certains aliments, les médicaments, les produits chimiques industriels, etc. Ces corps donnent lieu à des réactions dites anaphylactiques. Le deuxième groupe comprend les maladies qui s'accompagnent de sensibilisation à des produits toxiques en eux-mêmes, mais dont la toxicité est amplifiée par cette sensibilité qui résulte du contact avec ces produits. On compte parmi eux les micro-organismes, les virus et les parasites des animaux. Ils donnent lieu à des réactions du type "tuberculinique" qui sont des manifestations de la sensibilité à la fraction protéinique de ces corps. On les oppose habituellement aux réactions du genre anaphylactique, car elles sont retardées et prolongées au lieu d'être brutales, explosives et éphémères comme celles-ci.

L'hypersensibilité peut aggraver considérablement les effets de certaines maladies, comme entre autres la tuberculose. On avait antérieurement pris pour acquis que l'hypersensibilité est un mécanisme essentiel de l'immunité dans certaines infections comme la tuberculose mais les expériences de l'auteur ont démontré de plusieurs manières que l'hypersensibilité n'est pas nécessaire à l'immunité. Quand par exemple l'hypersensibilité est supprimée par la désensibilisation, l'immunité demeure intacte et l'atteinte tissulaire de l'hypersensibilité est évitée. Raffel a depuis montré qu'une forte hypersensibilité au B.K. peut être obtenue sans augmentation appréciable de l'immunité.

Les perfectionnements de la technologie de la vie moderne sont responsables de l'augmentation constante du nombre d'allergènes; les produits chimiques synthétiques employés dans la vie courante en grossissent le nombre chaque jour. L'apparition des sulfamides en fut un exemple frappant. Ces médicaments, d'un usage extrêmement répandu dans la thérapeutique contemporaine, peuvent s'attacher aux protéines pour former de nouveaux antigènes. Des études récentes ont permis d'apprécier qu'une grande variété de lésions de pathologénésie jusqu'alors obscure sont impliquées dans l'hypersensibilité aux médicaments et aux protéines étrangères. La périartérite noueuse en est un exemple typique. La sensibilisation aux protéines banales a permis en expérimentation animale de reproduire la maladie dans ses moindres détails, et plus récemment, on a découvert que chez le rat, l'hypertension, quelle qu'en soit la cause, entraîne l'apparition de lésions semblables. Le rat est le seul animal de laboratoire chez qui l'hypertension crée de telles atteintes vasculaires. Il va sans dire que l'hypersensibilité n'est pas la seule cause de la périartérite, car on l'a vu surgir à la suite de troubles circulatoires, soit dans la petite circulation après des embolies pulmonaires, ou dans la grande circulation dans les artères mésentériques après correction d'une coarctation de l'aorte. Lorsqu'une médication semble être la cause d'hypersensibilité, il est impératif de l'interrompre dès les premiers signes sous peine des conséquences les plus graves. Cette hypersensibilité a déjà été la cause de pneumonies dans lesquelles les capillaires alvéolaires endommagés laissent suinter le sérum et même les éléments formés du sang. On a déjà vu également des myocardites d'origine médicamenteuse en tous points semblables à celles que l'on observe dans la maladie du sérum. Certaines manifestations viscérales ressemblent à des lésions tuberculeuses en ce qu'elles comprennent des cellules géantes et des cellules épithélioïdes.

Le rôle du streptocoque dans la néphrite aiguë hémorragique a été soupçonné longtemps. L'auteur prétend avoir obtenu des lésions typiques chez des lapins en introduisant dans leur circulation une quantité suffisante de protéine (sérum de cheval ou blanc d'œuf) pour amorcer la production des anticorps et de l'hypersensibilité. Une néphrite expérimentale a même déjà été réalisée chez des sujets neufs par le transport passif des anticorps d'un animal sensibilisé; on voit alors apparaître une néphrite en 48 heures si l'antigène est introduit continuellement à petites doses par perfusion intraveineuse. L'A.C.T.H. et la cortisone protègent l'animal des lésions rénales expérimentales de la néphrite à condition d'être administrées dès le début de l'expérience. Rien de semblable n'a pu être réalisé chez les humains jusqu'à présent: les hormones ne sont d'aucun secours si on ne les emploie qu'à la phase oligurique.

Parmi les collagénoses avec atteinte vasculaire, on peut ranger le rhumatisme articulaire aigu. On a récemment remarqué que dans les tissus normaux ou en état de simple inflammation aiguë, la quantité d'albumine est plus grande que celle des globulines alors que dans les collagénoses il y a toujours un excédent de globulines sur l'albumine. Que penser de cette concentration de globulines? Serait-ce une agglomération d'anticorps? Nous n'en avons pas encore la preuve définitive. On a cependant noté que les malades souffrant d'agammaglobulinémie seraient exempts de collagénose. Le collagène normal dont la structure apparente semble homogène est en réalité composé de faisceaux de fibres striées d'après la microscopie électronique. Dans les réactions anaphylactiques, elles perdent ces stries et dégénèrent. Tous les essais cherchant à reproduire ces altérations par l'injection d'histamine dans les tissus ont échoué.

Les découvertes récentes en allergie ont peut-être fourni la réponse à quelques vieux problèmes, mais elles en ont par contre soulevé un grand nombre de nouveaux dont on ne soupçonnait même pas l'existence il y a quelques années.

EFFECT OF EXERCISE UPON THE MEAN DIASTOLIC LEFT ATRIAL-LEFT VENTRICULAR GRADIENT IN MITRAL STENOSIS

In the past, right heart catheterization has provided a valuable though necessarily limited view of the abnormal hæmodynamic state existing in patients with mitral stenosis. The development of left heart catheterization has afforded a more direct approach to disturbed physiology. Combined simultaneous right and left heart catheterization has been the next logical developmental step, for it permits more precise physiologic interpretation of the meaning of the left atrial-left ventricular gradient in terms of cardiac rate and flow across the valve.

In the present study, combined right and left heart catheterization at rest and exercise was performed 15 times in 14 patients with mitral stenosis. Measurements of cardiac output, heart rate, and mean diastolic left atrial-left ventricular gradients were carried out. For left heart catheterization, percutaneous puncture of the left atrium was carried out using two needles, through which small catheters were threaded. The needles were then removed.—R. S. Litwak *et al.*: *J. Thoracic Surg.*, 34: 449, 1957.

SPINOCEREBELLAR DEGENERATION: A CLINICAL SURVEY OF 74 CASES

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THE SPINOCEREBELLAR degenerations have become the subject of renewed interest because of the observation in recent years that, in some instances, the onset of symptoms may be associated with malignancy,[1, 2] chronic alcoholism[3, 4] and various other constitutional disorders, suggesting the possibility of a metabolic factor in the etiology. Greenfield[5] recently published a monograph giving an excellent review of this group of disorders with an attempt to classify the hereditary ataxias on the basis of histopathology. However, from the standpoint of the clinician and the student the multiplicity of terms, including many eponymous ones, used in textbook classifications is confusing and there is a general impression that considerable clinical variation is a common experience. Because we have been impressed in recent years with the essential similarity in clinical findings in a number of adult patients, we decided to review the cases seen at the Toronto General Hospital during the past 25 years, to determine the relative frequency of clinical variants that had been encountered.

We found 74 cases which were sufficiently well documented for us to exclude other disease entities and be reasonably sure that they were all examples of this disorder. The case histories had been filed under a variety of diagnostic terms including cerebellar ataxia, cerebellar degeneration, olivopontocerebellar atrophy, cortical parenchymatous cerebellar atrophy, progressive cerebellar atrophy, primary cerebellar atrophy, Friedreich's ataxia, etc. After analyzing the cases it became clear that different terminology often was used for cases showing almost identical clinical features. Greenfield[5] has divided the cases into three groups, i.e. predominantly spinal, predominantly spinocerebellar and predominantly cerebellar. From a clinical standpoint this classification is very practical and satisfactory. While certain minor clinical differences may exist between the different types that have been described within these groups, and pathologically the extent and location of the lesions vary to some degree, the boundaries separating them are, with certain exceptions, ill-defined.[6]

The clinical findings in these 74 cases indicated that they all belonged to one of two main groups, predominantly spinal or predominantly cerebellar (Table I). The various subgroups under these two broad headings will now be briefly considered.

TABLE I.—74 CASES OF SPINOCEREBELLAR DEGENERATION

1. Predominantly spinal degeneration		*12 cases*
(a) Friedreich's ataxia	8	
(b) Atypical Friedreich's ataxia	2	
(c) Hereditary spastic paraplegia	2	
2. Predominantly cerebellar degeneration		*62 cases*
(a) With family history	10	
(b) Without family history	52	
No additional factor	27	
With senility	7	
With adjuvant factors—18 (see Table II)		

1. PREDOMINANTLY SPINAL DEGENERATION

Friedreich's ataxia.—Only eight cases definitely conformed with the clinical syndrome of Friedreich's ataxia. This small number was a surprise, but may be explained in part by the fact that we are dealing with an adult hospital population. In only four instances was a family history of the disease obtained. The average age of onset was 11 years and the time of examination was 19 years. All the patients showed an ataxic gait with incoordination of all four limbs. Dysarthria was marked in six, nystagmus was present in four, decreased or absent tendon reflexes in four, pronounced pes cavus with or without kyphoscoliosis in five, deep sensation impaired in lower limbs in four, and dorsiflexor plantar responses in seven. Chronic myocarditis is occasionally an accompaniment of Friedreich's ataxia[7] and two of these patients showed evidence of cardiac disease. In both instances the electrocardiographic changes were similar to those that may be found after recent infarction. None of the patients had optic atrophy or Charcot-Marie-Tooth peroneal atrophy, both of which sometimes accompany Friedreich's ataxia.[8]

There were two other cases, both in males, that had been diagnosed as Friedreich's ataxia but were atypical and perhaps conform best with what has been called the Roussy-Lévy syndrome,[9] or hereditary areflexic dystasia.[10] This condition is probably a variant of Friedreich's ataxia, the main difference being the absence of early marked progression which is so characteristic of the latter. A brief summary of the two case histories follows:

CASE 1.—Onset of ataxia at age 20 but able to remain active for many years. When first seen at age 66 had been unable to walk for 15 years. Examination showed pes cavus, severe incoordination of the legs, loss of deep sensation in the lower limbs, dorsiflexor plantar responses and dysarthria.

CASE 2.—Onset of symptoms at age five led to investigation at the Hospital for Sick Children, Toronto. At this time the findings included ataxic gait, intention tremor of the left arm and dorsiflexor plantar responses. When seen at age 27 there had been some gradual progression of the incoordination in the limbs. Additional findings were pes cavus and scoliosis.

While these two cases have certain characteristics of Friedreich's ataxia, they differ in the long course after the onset without severe disablement.

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The other two spinal cases were examples of the variant known as familial spastic paraplegia. These were in two brothers, aged 47 and 32 respectively, and it was learned that a number of relatives, including their mother and two sisters, had the same condition, which had become manifest in early life in all instances and then slowly progressed. Both patients showed spastic weakness of the lower limbs with no sensory changes or any signs indicating cerebellar disorder. One had in addition some evidence of pyramidal tract involvement in the upper limbs and a very active jaw jerk.

2. PREDOMINANTLY CEREBELLAR

(a) *With family history.*—There were 10 patients, six men and four women, with a definite family history of the disease, involving siblings, parents and in one instance a grandparent. A wide range in age of onset was found, from 23 to 66 years, the average being 46 years. The course in general was long and slow. The findings included ataxic gait, incoordination of the arms, and dysarthria in all. Nystagmus was present in only two cases and these happened to be in sisters. One patient had an irregular tremor of limbs and head. The tendon reflexes were absent in the legs in one patient and two had dorsiflexor plantar responses. None showed any sensory impairment nor was there any significant mental change in any of these patients.

Two brothers, aged 56 and 51, will serve to typify the findings in this group. The onset occurred at age 39 and 46 respectively, and years later when they came under observation both had dysarthria, severely ataxic gait and incoordination of upper limbs. There was no nystagmus. Each had a profuse crop of prematurely gray hair. No other family history was obtained. It is of interest that the younger brother, who developed his symptoms at a later age than the other, had been a heavy consumer of alcohol for most of his life.

(b) *Without family history.*—There were 27 cases with predominantly cerebellar signs in which no family history was obtained and where there was nothing to suggest that any extrinsic factor was operative. Seventeen were males and 10 were females. The age range was similar to the former group, with an average age of onset of 51 years. All had ataxia of the legs as the most prominent symptom. All but three had incoordination of the upper limbs as well. Nineteen had dysarthria and 18 had nystagmus. Five had dorsiflexor plantar responses and one had absent reflexes in the legs. Failure of memory was marked in two cases. One patient had static tremor of the head, one had choreiform movements of the face and hands and one had an extrapyramidal type of tremor of all four limbs and head. Pneumograms in 10 of these patients revealed definite evidence of cerebellar atrophy in seven. The following brief history is from a case that typifies this group.

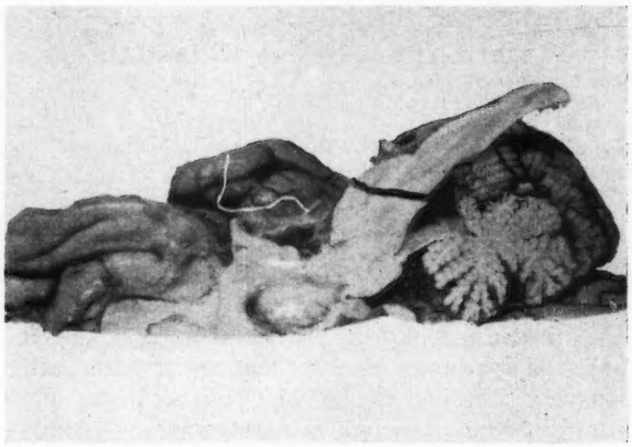

Fig. 1.—Case 3. Longitudinal section through brain stem and cerebellum showing atrophy of cerebellum and enlargement of fourth ventricle.

CASE 3.—This man, aged 67, had the onset of an ataxic gait at age 64 which was slowly progressive. Examination revealed a slurring dysarthria, nystagmus and incoordination of all four limbs, much greater in the legs. The reflexes in the legs were very active and both plantar responses were dorsiflexion. The cerebrospinal fluid was normal in all respects. The electroencephalogram was normal. Pneumography revealed a very large cisterna magna and an enlarged fourth ventricle. At postmortem three years later there was found to be severe atrophy of the cerebellum with extensive loss of Purkinje cells and less severe loss of granular cells, most marked in the vermis (Figs. 1 and 2). There was very marked demyelination and gliosis of the subcortical white matter.

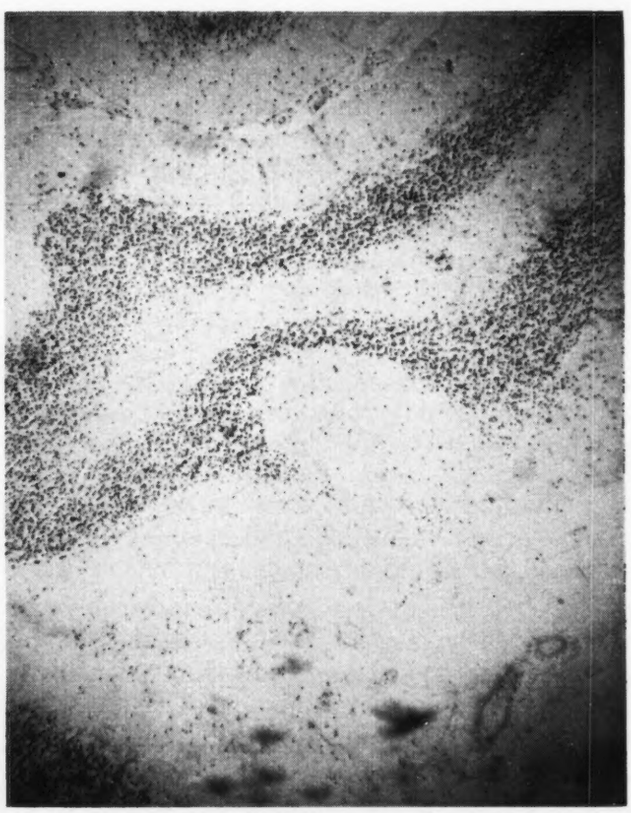

Fig. 2.—Case 3. Cerebellar cortex × 60. The cerebellar cortex is about half normal thickness and the Purkinje cells are few and pyknotic.

In general these patients with no family history did not differ essentially from those in this series with a family history as regards age of onset, course or findings. It may be that the failure to obtain a family history in some instances was because the disease had skipped one or more generations; also the tendency for patients to deny hereditary neurological disease is well known. Pathologically it is probable that the lesions vary only in extent, the cerebellum and its connections showing the most marked involvement in all cases. There was little to indicate spinal cord involvement, apart from upgoing plantar responses in some instances. No attempt has been made to break such cases down into various subclassifications, since these have been based largely on pathological findings. Attempts to separate them clinically on the basis of one or two signs are only confusing and serve no useful purpose. However, it might be said that a number of the patients conform with what has been described as "late cortical cerebellar atrophy" in the age of onset, course and clinical findings. Several cases were diagnosed as "olivopontocerebellar atrophy", but we doubt that this pathological entity can be recognized clinically except in rare instances.[12, 13] Extrapyramidal features of rigidity and tremor are perhaps a distinctive feature,[14] but only one case in this series showed these signs. This patient had superimposed on the findings of cerebellar disease a slow rhythmic parkinsonian tremor involving all four limbs and the head.

Senile cases.—In seven cases, all in males, the age of onset and the associated intellectual impairment suggested that degenerative changes associated with the aging process might be a factor in the cerebellar degeneration. The average age of onset was 66 years. Six of the patients were grossly demented and two had signs of severe arteriosclerotic cardiovascular disease. All had an ataxic gait as the major complaint. Incoordination of the upper extremities was found in five, static tremor of the head in two, dysarthria in two and nystagmus in one. Only one case had a pneumogram, and this showed gross enlargement of all ventricles, interpreted as indicating cerebral and cerebellar atrophy. There follows a brief history of a patient in this group.

CASE 4.—This man, aged 72, began to have an unsteady gait at age 63 which steadily progressed. Within a year or so of the onset there developed emotional instability, slurred speech and slowly progressive deterioration of memory. On examination he was irritable with severe memory defect. There was marked incoordination of both lower limbs with a very ataxic gait. The upper limbs showed incoordination on voluntary movement with intention tremor. Vibration sense was impaired in the lower limbs and ankle jerks were absent. Blood pressure and skull radiographs were normal.

It would seem probable that there is a vascular factor in the cerebellar degeneration in these cases, but their separation from the previous group is largely arbitrary, since there are no significant clinical differences in the manifestations of cerebellar degeneration. It may be that these patients have the same inborn tendency to cerebellar degeneration as the others and that the development of cerebral arteriosclerosis simply acts to precipitate the intrinsic fault into activity. On the other hand it is possible that the occurrence of senility with the cerebellar degeneration is only coincidental.

Cases with adjuvant factors existing.—Various disorders which may have contributed to the development of the disease in 18 of the cases are shown in Table II.

TABLE II.—WITH ADJUVANT FACTORS EXISTING—18 CASES

Alcoholism	7
Nutritional	2
Malignancy	4
Pernicious anæmia	2
Head injury	2
Nephritis	1

Alcoholism.—A history of marked alcohol addiction preceding the onset was obtained in seven instances. The average age of onset was 47 years. All showed severe ataxic gait, five had incoordination in the upper limbs, five had dysarthria and two nystagmus. The cerebellar disease was not accompanied by other forms of alcoholic encephalopathy in these patients and only two showed any evidence of peripheral neuropathy. It is of interest that one of these heavy drinkers had experienced rapid progression of ataxia during the year before his first examination. He became abstinent at this time and when examined one year later it was found that no further progression had taken place.

Following is the summary of the history of one of this group.

CASE 5.—Club steward, aged 54. This patient had been a heavy whisky drinker for many years, consuming at least a bottle daily. Sometimes he would go without food for several days while drinking. In 1952 there was a gradual development of an ataxic gait, clumsiness of the left upper limb and later dysarthria. Examination in 1955 revealed some impairment of memory for recent events, slurred speech, a reeling ataxic gait and incoordination of both arms, more marked in the left. There was no nystagmus. Pneumograms showed as the only abnormality enlargement of the fourth ventricle.

Nutritional.—In two cases a history of long-standing inadequate nutrition was obtained and, although alcohol was not a factor, the mechanism for the development of symptoms may have been of a similar nature. These two men both showed severe ataxic gait, incoordination of the upper limbs and nystagmus. One had dysarthria as well.

The history of one of these cases will be briefly summarized.

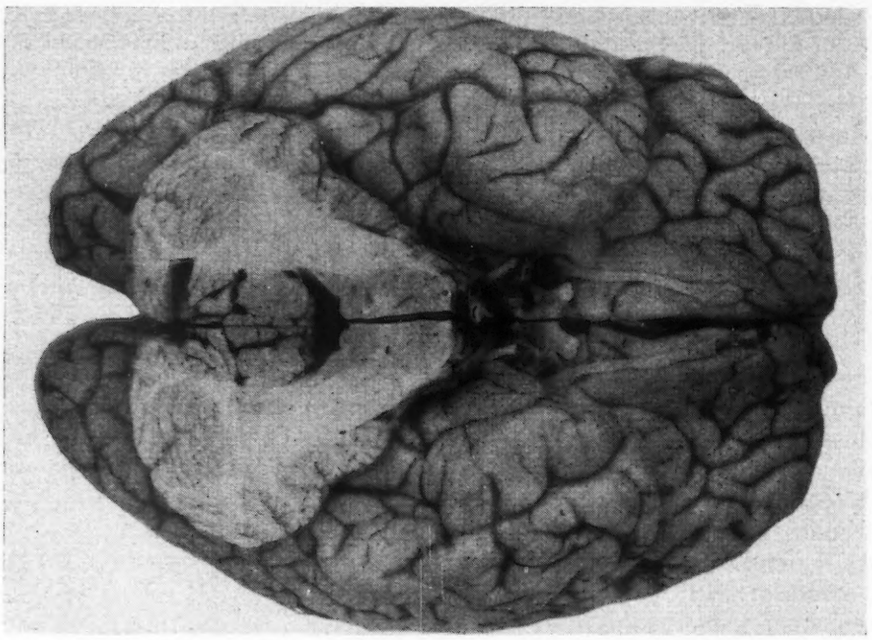

Fig. 3.—Case 8. Cross-section through cerebellar hemispheres and brain stem. Marked generalized atrophy of the cerebellum is present with enlargement of the fourth ventricle.

CASE 6.—This man, aged 54, who was mildly psychologically disturbed, worked as a baker. Commencing in 1920 he took an inadequate and deficient diet. Gradually over the years he lost more than 40 lb. in weight. The onset of ataxia was insidious and rather indefinite, but by 1944 unsteadiness in walking was quite evident. Beginning in 1946 he had frequent falls due to gradually increasing ataxia and by 1949 he was unable to do his usual work.

Examination in hospital in 1951 revealed him to be poorly nourished with nystagmus and incoordination of the upper and lower extremities and with intention tremor of both hands and a very ataxic gait. The reflexes were generally diminished. Pneumography revealed enlargement of all ventricles, in particular the fourth. He was seen again in 1956, but no subjective or objective differences from the previous examination were detected. He had been persuaded to take an adequate and balanced diet in recent years.

Malignancy.—Brouwer and Biemond[1] in 1938 first suggested a possible relationship between cerebellar ataxia and malignant disease. Often in such cases the course tends to be rapid, reaching complete incapacitation in one to two years, but the character of the symptoms is similar to that found in other types. It has been pointed out frequently that the malignancy may be clinically latent when the signs of cerebellar disease first appear.[5]

We found four cases with cerebellar ataxia in which malignant tumours situated respectively in breast, uterus, bladder and lung were verified following the onset of symptoms. In three of these the development of the cerebellar ataxia was more abrupt and the course more rapid than in the usual cases of cerebellar ataxia. In these three cases the diagnosis of malignancy was made within a year of the onset of symptoms of cerebellar ataxia. Following is a summary of one of these cases.

CASE 7.—This woman, aged 47, developed symptoms and signs of cerebellar disease so rapidly in 1954 that a tumour was initially considered. Her symptoms consisted of dysarthria followed within a few weeks by unsteadiness on her feet and then soon after by clumsiness of her upper extremities.

Examination two months after the onset revealed grossly slurred speech, incoordination of both arms, an ataxic gait, hyporeflexia, and bilateral dorsiflexor plantar responses. Pneumogram revealed no abnormality, the ventricular system appearing normal. The C.S.F. protein was 27 mg.%. General physical examination, including examination of her breasts, was negative.

About eight months after the onset she became aware of a growing mass in her left breast, which proved on operative removal to be adenocarcinoma. During the 10-month interval between examinations the only change in her neurological picture was one of progression of her previous manifestations of cerebellar disease to a degree that she was completely disabled and bedridden.

There was another case in which the onset and course of the cerebellar ataxia was very gradual and the evidence of carcinoma did not appear until several years after the onset.

CASE 8.—This man, aged 63, was first examined in 1942 when he gave a four-year history of occasional unsteadiness in walking. He showed only an ataxic gait and nystagmus. During the next four years the ataxia progressively increased and dysarthria developed. From 1943 on he was being treated by an outside physician for "prostate disease". In 1945 there was gross hæmaturia, following which his general condition deteriorated until death in 1947. At postmortem a papillary carcinoma of the bladder with secondaries in the lungs, liver, lymph nodes and spine was found. There was marked generalized atrophy of the cerebellum with enlargement of the fourth ventricle, and some atrophy of the pons (Fig. 3). Microscopic examination of the cerebellum revealed a narrow molecular layer with severe loss of Purkinje cells and moderate destruction of granular cells. There was diffuse gliosis in the molecular layer and slight gliosis of the white matter. The dentate nuclei showed no loss of nerve cells.

The seven-year interval between the onset of cerebellar symptoms and the symptoms clearly indicating malignancy makes it doubtful whether any relationship exists between the two conditions. The pathological finding of diffuse cortical cerebellar atrophy is similar to that described in other cases where malignancy has been implicated, but it is similar also to what was seen in Case 3 where

no adjuvant factor was present. It is possible of course that the papillary carcinoma might have existed in the bladder for a considerable time before the appearance of hæmaturia and have been a factor in causing the cerebellar degeneration. For that reason we have included the case in this group.

Pernicious anæmia.—In two cases pernicious anæmia may have been a factor in the development of cerebellar degeneration. One of these had the signs and symptoms of subacute combined degeneration as well. Both patients had been receiving inadequate therapy for their pernicious anæmia at the time of onset of cerebellar ataxia, but the incoordination of all four limbs and dysarthria which developed were unimproved when adequate liver therapy was administered. A summary of one of these cases follows.

CASE 9.—Age 67. The diagnosis of pernicious anæmia was first made in 1929. From this time until 1936 the patient took liver by mouth in inadequate amounts. Although he had had symptoms suggesting subacute combined degeneration for some time, his readmission to the Toronto General Hospital in 1936 was primarily because of the rather rapid development of ataxia during the previous two months. On examination he showed dysarthria, incoordination of both upper limbs and intention temor together with a severe ataxic gait and incoordination of both lower limbs. There were as well signs in the lower limbs indicating posterior column and pyramidal tract involvement characteristic of subacute combined degeneration of the spinal cord. The blood findings were typical of pernicious anæmia. On treatment with liver extract intramuscularly the subjective and objective manifestations of pernicious anæmia and subacute combined degeneration improved but the signs of cerebellar dysfunction remained unchanged.

Head injury.—A history of injury, not necessarily to the head, preceding the onset of symptoms of cerebellar ataxia is occasionally obtained and its significance may be difficult to evaluate. However, in two of our patients, both middle-aged males, the time relationship of the head injury to the onset of symptoms seemed too close to be coincidental. The symptoms of progressive cerebellar disease became manifest within two months in both instances. Following is a summary of one of the cases.

CASE 10.—This man, aged 64, had sustained a moderately severe head injury four years previously. On commencing to walk, after five weeks in bed, he noted that he staggered. This progressed during the next two years to a degree where he was unable to walk without support. Examination revealed nystagmus, slurred speech and gross incoordination of the lower limbs so that he was practically confined to a wheel chair.

Nephritis.—There was one case in which the disease developed insidiously while the patient was disabled with long-standing nephritis.

CASE 11.—This woman, aged 40, had been ill with subacute glomerulonephritis and mucous colitis which had become increasingly severe since childbirth in 1938. The blood pressure was normal. Her symptoms of cerebellar ataxia which began in 1943 were masked by the prostration associated with her nephritis and anæmia and were thought to be neurotic in origin until the correct diagnosis was established in 1946. At this time she showed nystagmus, a grossly ataxic gait and incoordination of all four limbs with hypotonia.

DISCUSSION

These 74 cases of cerebellar ataxia encountered in adult general hospital practice fall into two main groups: those developing in childhood where manifestations indicate that the spinal cord is the principal site of involvement and those developing in adult life where the cerebellum is predominantly involved. While the former group has certain well-defined clinical variations, the latter, which is much the larger group, tend to follow a fairly uniform pattern both in regard to course and to physical findings. Table III gives the main clinical features in the 62 cases where the cerebellum was predominantly involved. With the exception of those cases developing in senescence, where the average age at onset is much later and the incidence of dementia high, the clinical manifestations show little significant difference. There are many pathologically verified cases in the literature with various clinical signs in addition to those of cerebellar deficit, but such cases were rare in this series. Often such variants are found in families with the disease, but they may appear in sporadic cases also. Mental impairment or extrapyramidal features are perhaps the commonest but, apart from the patients with senility, there were only two in this series who showed definite intellectual deterioration and there was only one case with an extrapyramidal type of tremor in addition to cerebellar ataxia. Therefore it appears that cases with these or other added features are not common.

TABLE III.—FREQUENCY OF SIGNS IN CASES PREDOMINANTLY CEREBELLAR

	With family history	*No family history*	*With senility*	*With adjuvant factors*
	10 cases	*27 cases*	*7 cases*	*18 cases*
Average age at onset	46 years	51 years	66 years	53 years
Ataxic gait	100%	100%	100%	100%
Incoordination of upper limbs	100%	88%	70%	65%
Nystagmus	20%	66%	15%	47%
Dysarthria	100%	70%	30%	65%
Dorsiflexor response	20%	18%	80%	16%
Dementia	0%	7%	85%	0%
Choreiform mvts. or parkinsonian tremor	0%	7%	0%	0%

The number of cases in which a family history was obtained is surprisingly small, but the possibility of a genetic factor in the apparently sporadic cases cannot be excluded. In addition to intrinsic

factors, such as heredity, which may in some way be related to inherited deficiencies in certain enzyme systems, certain extrinsic factors seem to act as adjuvants in some instances. There were 18 such cases in this series where the symptoms appeared to be initiated clinically by the occurrence of another disorder. Greenfield[5] has stated that the term abiotrophy applies to the spinocerebellar degenerations if used in Gowers's sense as "a slow decay of the nerve elements which have a common function, a decay limited to these but extending throughout their entire extent". He believes that it is still legitimate to use the term in Gowers's sense for systemic degenerations which appear to be related to metabolic disturbance, such as avitaminosis or cancer, until a more complete explanation of their pathogenesis is forthcoming. Whether such patients would develop cerebellar degeneration in the absence of the added metabolic or other insults we do not know, but it would seem likely that some other factor exists since the number of patients with alcoholism, cancer, etc., who develop cerebellar ataxia is so relatively small. Brouwer and Biemond[1] suggested that the adjuvant factors may act upon a cerebellum which has an inherent tendency to degeneration, but Greenfield[5] points out that the difference in distribution of the lesions in most cases of diffuse cortical cerebellar atrophy from those found in hereditary cases does not support this hypothesis.

We do not know whether the cerebellar degeneration that may follow prolonged alcoholic excess is initiated by the toxic effect of the alcohol or whether it is essentially a nutritional deficiency, but, by analogy with alcoholic peripheral neuropathy, Wernicke's encephalopathy and Korsakoff's psychosis, vitamin B deficiency would seem to be implicated. There is also the possibility that cerebellar atrophy may develop after nutritional deficiency independent of alcohol, as suggested by two cases in this series. It is known that cocarboxylase from thiamin is essential for the decarboxylation of pyruvic acid to provide energy for cellular function in the central nervous system,[15] and abnormalities in the pyruvate tolerance test have been noted by more than one writer.[18]

Whether malignancy, elsewhere in the body, may act to deprive tissues of the central nervous system of enzymes essential for their nutrition is still not proven.[16, 17] It has been suggested that pantothenic acid may be incriminated in the sensory neuropathy which is occasionally found with bronchogenic carcinoma.[16] There is the possibility of deficiency of coenzymes necessary for certain reactions in the Krebs cycle energy transfer essential for the metabolism of cells in the central nervous system. Competition by tumour cells for such material, and release of an "anti-enzyme" or neurotoxin by the tumour cells, are possible explanations for its deficiency in the nervous system and the resulting degenerative processes that may occur in some patients with carcinoma.

Pernicious anæmia, chronic nephritis and head injury were other conditions which appeared to initiate the onset of cerebellar ataxia in some cases of this series, but we have no suggestions as to how these seemingly unrelated disorders could act to do so. One is almost forced to assume an inherent predisposition to cerebellar degeneration in such patients and to regard the added insult as in some manner "tipping the balance". The wide variety of diseases with which the onset of cerebellar degeneration may be associated have in common only that they cause a deterioration in the general state of health. This suggests that constitutional stress may play a part in initiating the activity of a latent tendency to cerebellar degeneration in patients who develop this disorder under such circumstances.

SUMMARY

Seventy-four cases of spinocerebellar degeneration seen in adult hospital practice have been reviewed. Clinically the cases fall into two main groups: predominantly spinal and predominantly cerebellar.

While the predominantly spinal group developing in childhood had distinctive clinical characteristics that served to differentiate the cases, the much larger predominantly cerebellar group, where symptoms became manifest in adult life, showed a surprisingly consistent pattern in regard to clinical manifestations.

Only 10 of the 62 patients in the predominantly cerebellar group had a family history of the disease. Apart from seven sporadic cases occurring in senescence, where the age of onset was late and the incidence of dementia high, there were no significant differences in age of onset, course or clinical findings between the sporadic cases and those with a family history.

In 18 of the cases various constitutional disorders existed which in some way may have determined the onset of cerebellar ataxia. These adjuvant factors have been described and their possible significance discussed.

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RÉSUMÉ

Les auteurs de cet article ont entrepris de dépouiller les dossiers de 74 cas d'hérédodégénération spino-cérébelleuse tirés des archives de l'Hôpital Général de Toronto. Ces malades furent vus pendant les derniers 25 ans. Au point de vue clinique les cas se répartissent en deux groupes: celui à prédominance radiculo-cordonnale postérieure et celui à prédominance cérébelleuse. Dans la présente série, les manifestations cliniques du premier groupe débutèrent dans l'enfance et montrèrent une diversité de caractère que l'on ne retrouva pas dans le deuxième groupe où les symptômes firent leur apparition au cours de l'âge moyen et présentèrent une uniformité surprenante. On ne put obtenir d'antécédent familial de la maladie que chez 10 malades du groupe à manifestations cérébelleuses. Sauf pour les sept cas sporadiques ayant débuté dans la vieillesse et dont plusieurs étaient accompagnés de démence sénile, on ne put déceler de différence importante dans l'évolution de la maladie, ses manifestations cliniques ou l'âge du début, entre les dix cas précités et les autres. Les troubles constitutionnels qui existaient dans 18 cas peuvent avoir joué un rôle dans le déclanchement de la maladie. Ces facteurs prédisposants sont décrits dans le texte et les auteurs ont cherché à en déterminer l'importance.

THE RISING INCIDENCE OF SCURVY IN INFANTS*
A CHALLENGE TO THE PHYSICIAN AND THE COMMUNITY

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ALTHOUGH the treatment of scurvy was first documented in 1536 by Jacques Cartier[1] and its prophylaxis was laid down by the British Navy in 1804, significantly increased numbers of cases have recently been reported from various parts of the world (Germany,[2] United States[3]). In Canada, during the past few years, a decided rise in the incidence of infantile scurvy has been noted in the Toronto area and in Winnipeg.[4]

We propose to summarize the clinical findings, feeding histories and errors in diagnosis associated with 79 cases treated in the wards of The Hospital for Sick Children, Toronto, during the five-year period 1951-1955. We shall attempt to explain the increased incidence and shall propose remedial measures. In addition certain experiments concerning the effects of heat on the vitamin C content of orange juice will be described.

In reviewing the admissions for scurvy to The Hospital for Sick Children during the past 26 years (Fig. 1) it was observed that the average annual incidence was seven cases until 1953, whereas in 1954 there were 46 cases and in 1955 there were 25.

CLINICAL FINDINGS

The clinical findings in our cases are similar to those reported previously.[3, 5–7] Nearly 90% of the 79 patients were between six and 12 months of age. In a few the symptoms had appeared a few days before admission, but on the average they had been present for three weeks and were increasing in severity. Abnormal irritability was characteristically present and was noticed especially when the diaper was changed. More than half the infants lay in the typical "frog position" which often suggested a diagnosis of paralysis. A hæmorrhagic tendency was present in 50%. Although this most commonly occurred as hæmatomata around the teeth causing swollen blue gums, some infants had petechiæ, hæmaturia and other more serious hæmorrhages. The majority of the patients were anæmic, some severely so. Stepping of the costochondral junctions (Barlow's sign) was present in practically every patient. In only one case was clinically detectable rickets associated with the scurvy.

Of the 78 patients examined radiographically 65 showed varying degrees of scurvy in the knees or wrists. In some, the white line of Fraenkel, the zone of rarefaction in the underlying metaphysis and the typical ground-glass appearance of the trabeculæ were all evident. On occasion radiographs were taken during therapy. In some, calcification of the stripped-up periosteum was seen. We found that a few cases considered to be severely affected did not show the typical radiological evidence of disease. These patients had usually been ill for only a short time, an association previously reported by Kajdi *et al.*[8]

In most of the cases the diagnosis was readily made. In some the diagnosis was not established until the clinical response to treatment had been observed. In a few, other more obscure diagnoses were originally considered even though the patient was subsequently proven to have moderately advanced scurvy. Some of these patients were referred to this hospital as cases of poliomyelitis, neuritis, acute rheumatism, congenital dislocation of the hip, leukæmia, anæmia, spinal cord tumour, rickets, osteomyelitis, and muscular[9] dystrophy.

Infections, usually respiratory, were present in 45% of patients on admission. Such infections have been thought to unmask scurvy[3, 10] because of the extra demands for vitamin C under such circumstances.

When plotted on anthropomorphic charts, the average birth weights of the scorbutic group did not differ from those of the normal population. Although the average weight on admission was three pounds below that expected, nine babies were overweight.

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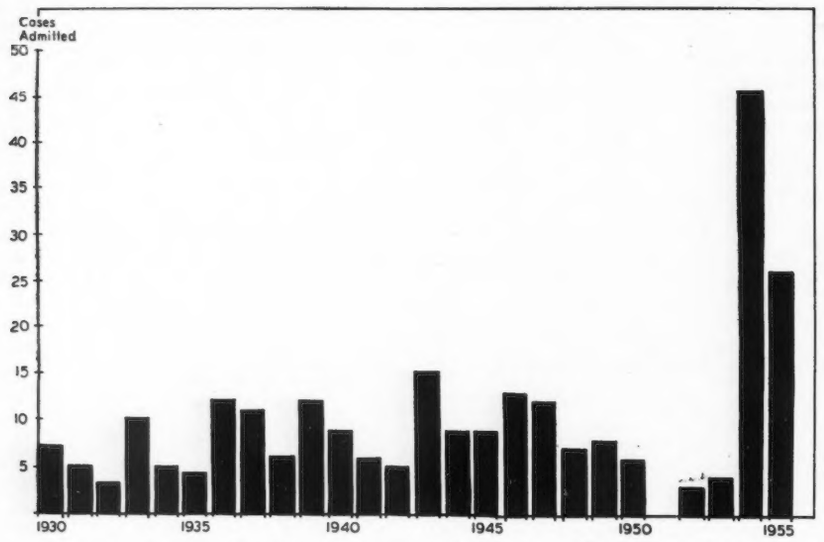

Fig. 1.—Cases of infantile scurvy admitted to The Hospital for Sick Children, Toronto, 1930-1955.

Half of the patients in this series lived in Toronto where medical advice was readily available from family physician, pædiatrician, or public health clinic; many of the others were referred from rural districts.

We did not find a convincing seasonal incidence in our group although Park *et al.*[11] described an increased number of cases in the autumn.

On reviewing the histories of the scorbutic infants it was noted that on the average there were three older children in the families. Scurvy had not been diagnosed in any of these older sibs. In only six instances was the affected child the first-born. This suggests that the earlier children were better fed.

The average duration of breast feeding in our cases was less than eleven days and none of our patients was receiving breast milk at the time of diagnosis.

The most suitable dietary sources of vitamin C for babies are orange or other citrus juices, or vitaminized apple juice. In 40% of our patients orange juice had been offered in the early months of life but lack of persistence was attributed to the child's reported dislike of orange juice or to the fact that he refused or "vomited" it when offered.

When questioned specifically, nearly 80% of the parents admitted that their child had received neither these juices nor synthetic ascorbic acid during the six weeks before diagnosis. In one child, orange juice and most other fruits and vegetables had been omitted because of severe food allergies; in another, severe thrush had prevented the infant from eating a normal diet. Thirty of the infants had received some other fruits or vegetables during the six weeks prior to the diagnosis of scurvy. The fact that these foods alone did not prevent the disease emphasizes how little ascorbic acid they contain.

Twenty per cent of the parents claimed to have given what would be considered adequate amounts of vitamin C. In seven instances the parents stated that boiling water had been added to the orange juice.

TREATMENT

The treatment of the scorbutic process was simple and the results were excellent, but the associated anæmia or infection often prolonged the stay in hospital considerably. The average period of hospitalization was 12 days, although it extended to 32 days in one case. The treatment consisted of the oral administration of high doses of vitamin C (average 300 mg. per day), usually given as orange juice and synthetic ascorbic acid in combination. In no case did large doses of orange juice cause any allergic reactions or gastro-intestinal upsets. From the time of admission the child was offered a full diet which included milk, cereals, vegetables, fruits, egg yolk, meats and a supplement containing vitamins A and D. By the time the child was improving clinically this diet was usually being taken well.

A few days after treatment was begun, the irritability and leg weakness were usually noticeably less and the abnormalities in the gums had almost disappeared. Occasionally a week or ten days elapsed before definite improvement.

In a small study of hospitalized scorbutic infants, carried out at this hospital some years ago, Snelling[12] states that small amounts of orange juice (two to four ounces) appeared to relieve the clinical symptoms more rapidly than equivalent amounts of ascorbic acid in synthetic form. The data from our study do not permit us to compare the efficacy of these two forms of therapy.

DISCUSSION

From the foregoing review it is evident that the clinical features in the present series of cases are typical. The aspect which requires explanation is the recent and alarming prevalence of the disease. Is this due to an increased requirement for vitamin C or to a diminished intake?

We do not believe that the recent prevalence of scurvy can be attributed to an increased vitamin C requirement, for the following reasons. The average growth rate of babies under nine months of age is greater now than 20 years ago but this increase would not raise the requirement for vitamin C appreciably. The fact that the incidence of scurvy has not increased in all parts of Canada[13–16] would support this contention. It has been shown that the requirement for vitamin C

is increased during infection, and in our series, infections were present on admission in 45%. However, this percentage is not higher than those reported by some other investigators.[2, 17]

What evidence is there that infants are now receiving less vitamin C than formerly? As mentioned previously, the average duration of breast feeding was less than 11 days in our group of patients and not one of the infants was being breast-fed when scurvy developed. Breast milk of a well-nourished mother contains considerable amounts of ascorbic acid (approximately 5 mg. per 100 ml.).[18] On the other hand the concentration in unpasteurized cows' milk is only 1.8 mg. per 100 ml.[18] During pasteurization the vitamin C content is reduced to about 0.6 mg. per 100 ml.[19] In the processing of evaporated milk even greater losses occur. The reconstituted product has been found to contain, on the average, 0.2 mg. per 100 ml.[19]

The parents of 80% of the patients admitted that their babies had not received any form of vitamin C supplement. The parents of the remaining 20% claimed that their infants had received what was considered adequate amounts of orange juice or synthetic ascorbic acid. We doubt this claim. The most convincing justification for our doubt lies in the fact that the scorbutic infants invariably improved rapidly when given therapeutic doses of vitamin C. It may be pointed out in addition that no authenticated instance of "vitamin C resistant" scurvy has ever been reported.

We believe that in many cases the parent was misleading her doctor and sometimes herself regarding the quantity of vitamin C actually ingested, possibly because she feared criticism. As an example one may cite the case of a mother with a low income and six small children who stated that she had given her affected child a full diet with one and a half ounces of orange juice daily since the age of two months. While in hospital, one of the nurse's notes read, "Infant will not take solids and has to be coaxed to take orange juice". The child improved rapidly when treated with orange juice.

VITAMIN C STABILITY

In seven instances the parent stated that the affected child had been given orange juice to which boiling water had been added. In order to determine whether such treatment produced a significant alteration in the vitamin C content of orange juice, we undertook a controlled series of experiments to assess the effect of heat on this vitamin.

The ascorbic acid concentration was determined by a modification of the dye-reduction method of Mindlin and Butler.[20] The ascorbic acid was extracted with 3% metaphosphoric acid and determined by measuring photometrically the amount of 2,6-dichlorophenolindophenol dye solution decolorized in a period of 10 seconds.

Determinations were made upon fresh, canned, and reconstituted frozen concentrated orange juice. In order to reproduce in an extreme form the modifications commonly practised in the home, each of the three forms of orange juice was subjected to boiling, alkalinization, and alkalinization followed by boiling.

Our results have shown that there was no significant difference in the content of vitamin C of the various untreated forms of orange juice, or in the way it was affected by the insults imposed. The concentration of ascorbic acid before treatment ranged from 40 to 65 mg. per 100 ml., which is in agreement with the figures reported by others[21]

When orange juice was diluted with an equal volume of boiling water and allowed to cool to room temperature there was no detectable decrease in the vitamin content. This supports the statement of Payne,[22] who found there was practically no destruction of vitamin C after boiling water was added to orange juice concentrate.

After the orange juice had been boiled for 40 minutes in an uncovered, chipped, rusty, enamelled saucepan, the ability of the sample to decolorize the dye ranged from 74.5% to 85% of the activity before boiling. In other words, only 15 to 25.5% of its vitamin C had been destroyed. The pH of the juice remained at 3.55.

Our results are in agreement with those of LaMer, Campbell and Sherman.[23] The latter authors, using a bioassay procedure,[24] found that approximately 68% of the vitamin C activity of tomato juice persisted after vigorous boiling for 20 minutes at a natural pH of 4.2 to 4.4 and that 50% of the original activity remained after one hour of boiling. Although bioassay offers the only specific method for the measurement of vitamin C activity, the chemical method of Mindlin and Butler has been shown to give a reliable estimate of the vitamin C content under ordinary conditions.

When we adjusted the orange juice to pH 7.3 by the addition of sodium bicarbonate, and allowed it to stand at room temperature for 30 minutes, there was no apparent change in its vitamin C content as measured by its ability to reduce the dye. The latter test was carried out because it was a common belief among mothers of the past generation that ordinary orange juice was too acid for the delicate stomach of the small infant.

An attempt was made to determine the effect of boiling on the vitamin C content of orange juice after it had been adjusted to pH 7.3. However, marked changes were observed in the behaviour of the dye complex under these circumstances. It is known that if carbohydrates are heated in alkaline solutions "reductones" are readily formed. It is presumed that the development of such unspecific reducing substances after boiling the alkaline orange juice accounted for our inability to make a satisfactory measurement of the vitamin C content under these conditions.

The difficulties inherent in the use of the dichlorophenolindophenol dye reduction method for the measurement of antiscorbutic activity in heat-treated alkaline solutions are eliminated in the bioassay procedure. When LaMer, Campbell and Sherman[23] tested the residual antiscorbutic activity of heat-treated alkalinized tomato juice in guinea pigs, they observed, as would be expected, some reduction in the vitamin C content. However, it is very significant to note that even when tomato juice, alkalinized with NaOH to

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pH 10.9, was boiled for one hour, 35 to 39% of its original antiscorbutic activity persisted.

This series of experiments serves to emphasize the stability of vitamin C in orange juice. Our findings indicate that dilution of orange juice with boiling water had no effect upon its ascorbic acid content and that at least 75% of the vitamin C survived long and vigorous boiling. Neutralization of orange juice a short time before estimation had no demonstrable effect on its ascorbic acid content.

Notwithstanding widely quoted statements to the contrary,[6, 17, 25] there can be little doubt that the antiscorbutic activity of orange juice will withstand the well-meaning but unnecessary manipulations of the most imaginative mother. It must be concluded that the parent's method of preparing the orange juice did not affect its antiscorbutic value significantly.

A review of the foregoing considerations has led us to the conclusion that, in every instance, the scorbutic state must be attributed to an inadequate intake of vitamin C. In attempting to explain this circumstance, one must consider, among other factors, the rapid sociological changes that have occurred in this country since the last war. Increasing immigration and the movement of people from farms to cities[3] create situations in the home which may well contribute to this new public health problem. Under the present conditions of home life, parents tend to spend less time with their children. The greater incidence of scurvy in children of later birth rank suggests that less care was taken to provide them with sufficient ascorbic acid.

Many of our cases were from economically poor homes; on the other hand, some were from the higher social and economic strata and were under the care of private practitioners. In recent years, there has been a conspicuous tendency among physicians in this area to recommend the use of synthetic vitamin preparations, which parents usually consider as medicine, instead of making orange juice a regular part of the baby's diet. Although there is no doubt that many of these preparations are effective in preventing scurvy, certain others contain no ascorbic acid. When faced with such an array of widely advertised, variously priced medications, it is not surprising that the mother may become confused. One cannot emphasize too strongly the necessity for specific designation of the trade name and the dosage to be used when vitamin preparations are substituted for orange juice. Many of the parents whose scorbutic children had been receiving fish liver oil preparations were surprised to learn that the latter did not supply all the vitamin requirements.

In past centuries, rickets was very commonly associated with infantile scurvy.[26, 27] This situation has changed greatly within the last few decades. In 1946, rickets was present in only 9% of Dogramaci's series of scorbutic infants.[5] In the present series, despite the fact that 59 infants had received no vitamin D supplement, evidence of rickets was observed in only one of the 79 patients. The disproportionate reduction in the incidence of rickets is probably largely attributable to the fact that in Canada almost all brands of evaporated milk are now fortified with considerable amounts of vitamin D.

RECOMMENDATIONS FOR PROPHYLAXIS AND TREATMENT

The recommended daily allowance of ascorbic acid for babies under one year of age is 30 mg.[28, 29] We prefer orange juice to synthetic preparations as the source of this vitamin. Starting at two weeks of age, infants should receive, daily, one teaspoonful of orange juice (fresh, frozen or canned) diluted with an equal amount of boiled water. The amount should be increased by one teaspoonful of each, twice weekly, until the baby is receiving one ounce of orange juice and one ounce of water. Thereafter continue to increase the orange juice at the same rate until, at two months of age, the infant is receiving two ounces of orange juice (diluted with one ounce of water). At one year of age the orange juice should be increased to three or four ounces daily.

Given as we have recommended, orange juice is well accepted and we believe that it rarely causes allergic reactions or gastro-intestinal disturbances. It is seldom necessary to resort to synthetic preparations to supply the ascorbic acid needs.

The recommended treatment for infants who have developed scurvy consists of six ounces of orange juice (about 175 ml.) plus 100 mg. of synthetic ascorbic acid daily for three weeks. Thereafter suitable daily prophylaxis should be instituted. The children reported in the present series were all admitted to hospital. However, the tendency since 1955 has been to treat uncomplicated cases in the outpatient department, and the results of this policy appear to be satisfactory. Considerable numbers of patients with scurvy are still being seen at this hospital.

It is obvious that to solve the problem of the rising incidence of scurvy the medical profession and the community must ensure that every infant receives at least 30 mg. of vitamin C daily. Instruction of the parent in this regard should be attempted by exploiting the following measures:

1. Use of the press, radio and other means of public communication to give parents a better understanding of the nutritional needs of the infant.

2. Emphatic and more specific advice from doctors concerning the value of orange juice in infant nutrition, and insistence upon one specific vitamin C supplement if sufficient orange juice is not taken daily.

3. Instruction of the parent by informed pharmacists concerning the vitamin C content of the various vitamin preparations on the market.

4. Re-emphasis by public health authorities and by the physician of the virtues of breast feeding.

5. The incorporation of vitamin C into certain foodstuffs commonly consumed by infants (compare the widespread addition of vitamin D to evaporated milk). In this regard, due consideration must be taken of the instability of vitamin C in non-acid solutions.

SUMMARY

A review is presented of the histories and clinical findings of 79 infants with acute scurvy who were admitted to The Hospital for Sick Children, Toronto. Forty-six of these were admitted during one year. This incidence constitutes a striking increase over former years.

Possible reasons for the recent increase in infantile scurvy are mentioned, and certain sociological factors are discussed. Of the various factors considered, it is concluded that, despite parental claims to the contrary, an inadequate intake of vitamin C was, in every case, the cause of the scurvy. In this regard, the present-day decline in the use of orange juice in infant feeding is thought to be correlated with the recent rise in the incidence of scurvy. We suggest that the modern policy of recommending multiple vitamin preparations may be less reliable in the prevention of scurvy than was the old custom of including orange juice in the infant's diet.

Experimental evidence is presented which disposes of the frequently expressed belief that the antiscorbutic effect of orange juice is destroyed by boiling. Recommendations for the therapy of acute scurvy are presented, and a five-point educational program is suggested to aid in the elimination of this readily preventable disease.

We wish to thank Dr. J. A. Keddy of the Department of Medical Records and Statistics, The Hospital for Sick Children, Toronto, for his assistance in making available the clinical data used in this review.

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RÉSUMÉ

Il est quelque peu vexatoire de constater que plus de 400 ans après l'épidémie de scorbut qui terrassa l'équipage de Jacques Cartier, les Canadiens souffrent encore de cette maladie. En effet, les auteurs de cet article rapportent une série de 79 cas de scorbut infantile traités au Sick Children Hospital de Toronto de 1951 à 1955. Jusqu'en 1953, la fréquence annuelle de ces cas s'établissait à sept; en 1954, elle atteignit 46. La plupart des petits malades étaient âgés de six à 12 mois; plus de la moitié d'entre eux venaient de la région métropolitaine de Toronto. Le tableau clinique était caractérisé par une irritation très marquée des nourrissons ainsi que par des manifestations hémorragiques dans 50% des cas. On nota aussi un bon nombre d'infections des voies respiratoires. Les diagnostics erronés posés avant que la maladie ne soit reconnue comprenaient: poliomyélite, névrite, arthrite aiguë, leucémie, ostéomyélite, dystrophie musculaire, etc. En retraçant les causes qui amenèrent cet état de chose, la raison la plus communément offerte fut le manque de persévérance des parents à offrir le jus d'orange que les enfants refusaient ou vomissaient au début. A leur admission à l'hôpital, 80% de ces malades n'en recevaient plus depuis des semaines. Le scorbut lui-même fut traité sans difficulté, mais il n'en fut pas toujours ainsi de l'anémie ou des infections associées.

Alors que l'allaitement maternel est une assez bonne source de vitamine C, les formules basées sur le lait de vache sont relativement pauvres en comparaison, surtout lorsqu'il est soumis à la pasteurisation. L'allaitement artificiel est encore plus dépourvu d'acide ascorbique si les formules sont basées sur le lait concentré par évaporation. Les auteurs ont prouvé que l'ébullition, la dilution ou l'alcalinisation comme on peut les pratiquer à domicile dans la préparation des biberons affectent très peu la teneur du jus d'orange en vitamine C. Certains produits pharmaceutiques destinés aux enfants comme les huiles de foie de poissons ne contiennent pas de vitamine C. Les auteurs recommandent le jus d'orange (frais, frigorifié ou en conserve) de préférence à la vitamine synthétique dans la prophylaxie du scorbut.

GASTRIC SECRETION AS INFLUENCED BY RAUWOLFIA ALKALOIDS

The effects of various rauwolfia alkaloids on gastric secretion were investigated. Intravenously, 1 mg. of reserpine evoked a significant and prolonged hyperchlorhydria. This response was not blocked by atropine, methantheline bromide, epinephrine or vagotomy. Oral doses of the various rauwolfia alkaloids induced gastric hypersecretion when given in large (2.5 mg.) single doses. Small or "average" single doses of these compounds did not influence gastric secretion, however. When *Rauwolfia serpentina* (200 mg./day) or reserpine (1 mg./day) was given over 14-day periods to normal volunteers, no significant alterations in gastric secretions or urine uropepsin excretion were noted, in comparison with placebos. *Rauwolfia serpentina* and phenobarbital had no greater value therapeutically in patients with duodenal ulcer or "functional" gastrointestinal disease than a placebo. The alkaloids or rauwolfia probably exert their stimulating action on the stomach locally rather than centrally. This activity may be mediated by serotonin. Although no proof of their being ulcerogenic exists, it would seem prudent to use large doses of the rauwolfia alkaloids with caution, especially in patients with peptic ulcer.

The real value of these agents, as regards the gastrointestinal tract, seems to rest in their usefulness for studying gastric secretory mechanisms.—E. M. Schneider and M. L. Clark: *Ann. Int. Med.*, 47: 640, 1957.

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CARBON MONOXIDE ASPHYXIA, A COMMON CLINICAL ENTITY

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CARBON MONOXIDE poisoning is not merely a curiosity described in public health textbooks, but a common occurrence often overlooked.

This is well illustrated in the following case.

CASE 1.—On July 25, 1953, a robust young garage mechanic fell unconscious while at work and was admitted to hospital. He recovered consciousness in a short time and complained of loss of power of his hands, paræsthesiæ in the extremities, blurring of vision, weakness and dizziness. A cerebrospinal fluid (CSF) examination was negative for cells and protein. He was discharged symptom-free in a few days.

He returned to his physician on August 3, 1953, complaining of dizziness and vertigo, and was referred for neurological consultation. A major investigation including encephalography and air ventriculography was negative. Barium meal and gall-bladder x-ray series were normal. Repeated complete blood counts and urinalyses were within normal limits.

During the next eight months he complained of four main symptoms: headache, anorexia, dyspepsia and tiredness. In the absence of positive physical or laboratory findings his trouble was considered of psychosomatic origin. In the course of several investigations his symptoms cleared without specific treatment.

On March 1, 1954, he was first interviewed by the author. When questioned as to his colour during the first attack, he recalled comments about his flushed appearance. The results of a routine physical and neurological examination were negative. Laboratory findings: complete blood counts and sedimentation rate, normal; urinalysis including tests for bile and urobilinogen, normal; Wassermann reaction, negative; 6-hour glucose tolerance curve, normal; cephalin cholesterol flocculation, negative after 48 hours; electrocardiogram, within normal limits.

Because the illness recurred whenever the patient returned to work in the garage, carbon monoxide poisoning was suspected. Spectrographic examination of a blood sample revealed 18.5% carboxyhæmoglobin.

The patient was taken off work and given inhalations of a mixture of oxygen (95%) and carbon dioxide (5%) (carbogen) one hour daily for a week. After the first treatment he noticed marked improvement, and he developed a hearty appetite. On March 21, the COHb was 10% and the patient was symptom-free. On April 9, the COHb was less than 5%.

A routine report was sent to the Workmen's Compensation Board (Saskatchewan), as it was now evident that the patient's disability arose out of an occupational hazard in his garage. This case was discussed at the annual convention of Canadian compensation boards in December 1954. None of the medical representatives could recall a previous claim for this condition.

In the past three years the author has had 30 personal cases of chronic carbon monoxide poisoning. The other members of our medical group contributed data on an additional 11 cases (Table I).

DISCUSSION

We have elected to diagnose as "chronic carbon monoxide poisoning" those cases which fulfil the following criteria:

(a) The blood level of COHb is 10% or more.

(b) Symptoms of vague ill health usually include one or more of: headache, anorexia, "dyspepsia", weakness, dizziness.

(c) The symptoms should clear four to seven days after removal from exposure and daily inhalations of "carbogen" for one hour. (The addition of CO_2 to the mixture increases the respiratory rate and facilitates the dissociation of COHb.)

(d) No other medication is necessary.

(e) The patient is symptom-free when the blood level of COHb is reduced to below 10%.

Our cases fell into three common environmental categories: (a) garage workers, (b) drivers of vehicles (trucks, tractors), and (c) housewives. The source of pollution in a garage needs no further mention. Routine COHb determinations are now done on all garage workers seen in our office. Results indicate that CO poisoning is a common cause of disability in this occupation.

In 1955 the Public Health Department of Swift Current in cooperation with the Workmen's Compensation Board undertook a survey of the local garages; this survey was extended to all the garages in Health Region No. 1. It was discovered that insufficient care was being taken to prevent exposure to carbon monoxide. Air exhaust equipment was not used regularly, and nearly all garages were inadequately ventilated. The air samples taken indicated that in most cases the CO levels were above or close to the maximum concentration allowed (0.01%). Most of the workmen interviewed stated that conditions were often much worse than at the time of testing. It was concluded that even average conditions would show a poorer test. The equipment used was an "M.S.A. carbon monoxide tester" (developed by the National Bureau of Standards, Mine Safety Appliances Co., Pittsburgh, Pa., and lent by the Saskatchewan Workmen's Compensation Board).

Operators of farm tractors accounted for a large number of cases. Many diesel farm-tractors have a vertical exhaust stack no higher than the driver's head. The driver may complain of headache and malaise after a prolonged period on the tractor.

In enclosed vehicles the source may be a defective manifold or muffler.

Housewives comprised 25% of our cases. Washing machines operated by gasoline engines are often used on farms in the district; their use in poorly ventilated rooms caused illness in some of our patients. In one instance the use of a gas-heated iron produced toxic concentrations of CO. A frequent offender has been a "space heater" type of oil stove located in the family living room. These oil burners, along with the larger forced-draft heating units, have a swinging draft at the

origin of the chimney which allows room air to be sucked in to cool the chimney and prevent the fire from being snuffed out by updrafts. During the windy winter of 1956 many cases of CO poisoning in the home occurred. Intermittent down drafts caused small amounts of fumes to leak past the swinging draft door, giving rise to poisonous levels of CO. Being constantly indoors, the housewife was most affected. These cases cleared rapidly when a Coleman "chimney cap" was installed.

DISCUSSION OF METHODS

All COHb estimations were done on venous blood which was mailed to the Provincial Laboratory at Regina. Two grams of sodium fluoride and two grams of potassium oxalate were added to 100 c.c. of distilled water. To each 5 ml. of blood was added 0.5 ml. of this preservative. The maximum delay in testing was 48 hours. All tests were done by the spectrographic method.

Whenever there was doubt as to the source of a patient's exposure, the spouse was used as a control; thus we could be reasonably sure of the offending area. After removal of the patients from the source, or alteration of a suspect environment, COHb determination was repeated in 10 to 14 days. If the COHb concentration became markedly reduced, we presumed this to be strong evidence in favour of our environmental diagnosis. The patients were instructed to report immediately for a blood test upon recurrence of symptoms, but apart from those in garage workers we saw no recurrences.

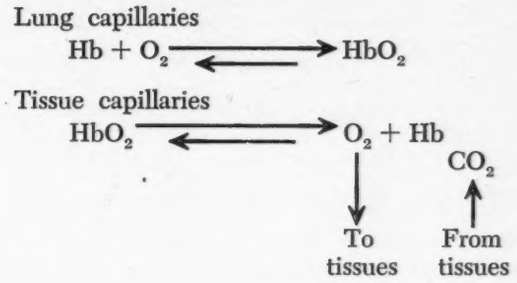
Cases 42 and 44 illustrate some of the problems in establishing a source. P.P.G. did not drive a private car; the truck he drove was new. Three CO determinations were done by the local public health department with the truck idling, the windows closed, and the heater on. The first test on the air inflow from the heater showed 0.05% CO; in two others none was detected. Mrs. P.P.G.'s blood showed no COHb. Prior to driving this truck, Mr. J.T. (a second driver) had a blood level of 17% COHb. At the end of one month his COHb rose to 24%. He was taken off work, whereupon the level dropped rapidly. The evidence incriminates this truck even though careful check failed to reveal a mechanical defect.

Toxicology of Carbon Monoxide

Carbon monoxide, an odourless, colourless and tasteless gas, results from the incomplete combustion or explosive burning of most fuels. It combines with hæmoglobin to form carboxyhæmoglobin (COHb) at a rate which in man is at least 210 times greater than the analogous reaction of oxygen with hæmoglobin (HbO_2).[2] The resulting compound (COHb) will not transport oxygen and inhibits the unbound hæmoglobin in this function.

In the first place, Hb in combination with CO is effectively removed from the circulation; the patient has now an "anæmia". In the second place (and this is the crux of the matter) the presence of COHb in the red blood cells completely distorts the chemistry of O_2 transport by the remaining Hb and its subsequent release in the tissues.

The normal state of affairs may be expressed by the equation:



Only slight changes in O_2 tension have a profound effect on the total amount of O_2 combined or released, respectively. The graph of this reaction is called a "dissociation curve". In the presence of COHb the following changes occur:

Tissue Capillaries

$$HbO_2 + COHb \rightleftharpoons O_2 + Hb + COHb$$

Now much lower tissue tensions are required before O_2 will move from the HbO_2 in the capillaries into the tissues. The patient is literally starving in a land of plenty. As an illustration, a death has been recorded with COHb saturation of only 30%.

The mechanism is complex but the result is always anoxia and nothing more. Long before the CO saturation builds up to the point where tissue respiration via the cytochrome oxidase system is affected, the patient is dead.[1]

The reasons why clinical symptoms are so precisely related to the COHb level are now apparent. Theoretically and clinically, when the COHb has disappeared or is reduced to a low level the symptoms are gone.

The role of CO_2 in the treatment is twofold. It has a physiological effect in increasing the rate and depth of respiration. It also has a purely chemical effect in helping to facilitate the reaction COHb $(+CO_2) \longrightarrow CO + Hb\ (+CO_2)$, i.e. COHb will dissociate more readily in the presence of CO_2.

Thus low blood concentrations of CO may exert a harmful physiological effect, especially during exertion accompanied by increased breathing rates. At ordinary altitude and barometric pressure, 0.01% in air by volume may be tolerated for several hours without perceptible effect at the normal lung ventilation rate of 10 litres per minute. However, 0.05%-0.07% may produce unpleasant symptoms in less than one hour. For prolonged exposure the permissible limit should not be greater than 0.01%, preferably less.

The general subject of carbon monoxide asphyxia has been reviewed at length by Drinker[2] and the effects at high altitude by Heim.[4] Drinker has made some interesting observations:

"Both city dwellers and smokers may have detectable quantities of CO in the blood under normal conditions. . . . Street cleaners working in New York showed an average of 3% COHb saturation. . . . Experiments on persons smoking continuously in a room for about two hours under conditions where the smoke became so thick that it was necessary to wear goggles after about one hour indicated that the highest blood saturations attained were no greater than about 5%. . . . Subjects chronically exposed to blast furnace gas had an average CO saturation in their blood of 6.3 to 7% after eight hours' work but in some of these individuals it was as high as 10 to

TABLE I.—CASES OF CHRONIC CO ASPHYXIA, SWIFT CURRENT, SASKATCHEWAN, 1954 - 1957

Case 1954	*Occupation*	*Source of CO*	*COHb*	*Headache*	*Anorexia, nausea*	*Weakness*	*Dizziness*
1. A.S.	Garage mechanic	Car exhaust	18.5%	++	++	++	+
2. A.F.	Garage mechanic	Car exhaust	15%	++	0	+	0
3. R.M.	Driver of road grader	Diesel engine, short exhaust stack	12.5%	0	+++	0	+
4. G.B.	Garage worker	Car exhaust	17%	++	0	0	0
5. A.K.	Garage worker	Car exhaust	12.5%	++	0	0	0
6. E.S.	Elderly widow	Space heater near bedroom	17%	+	+	+	+
7. S.S.	Physician	Space heater in bachelor suite	11%	+	+	0	0
1955							
8. A.K.	Garage worker	Car exhaust	12.5%	++	0	0	0
1956							
9. H.B.	Farmer	Gas engine washing machine	15%	++	+	0	0
10. Mrs. H.B.	Housewife	Same	18%	+	0	0	0
11. S.U.	Garage owner	Car exhaust	10%	+	0	+	0
12. C.O.	Garbage collector	Walking behind garbage truck	15%	+	+	0	0
13. E.M.	Elderly housewife, cardiac	Space heater	12.5%	+	0	0	+
14. Mrs. S.P.	Housewife	New forced draft oil furnace; checked for leaks—none found	21%	+	+	+	+
15. S.P.	Carpenter (control)		8%	0	0	0	0
16. W.O.	Driver of delivery truck	Truck stuck in snow. Pushed for ½ hour near exhaust pipe	15%	++	0	+	0
17. Mrs. W.O.	Housewife	Space heater in living room of trailer	10%	0	0	0	0
18. F.M.	Garage worker	Car exhaust	9%	+	0	0	0
19. C.M.	Garage worker	Car exhaust	17.5%	++	++	+	+
20. Mrs. J.W.	Housewife	New forced draft propane gas furnace tested for leaks; none found.	15%	+	+	++	+
21. J.W.	Carpenter (control)		less than 5%	0	0	0	0
22. A.T.	Farmer	Diesel tractor, short stack	12%	0	+	0	0
23. J.R.	Driver of delivery truck	Leaking manifold, defective muffler	12%	+	0	0	+
24. H.M.	Farmer	Space heater	10%	0	0	0	++ 3 mths.
25. Mrs. H.M.	Housewife		10%	0	0	0	0
26. R.H.	Housewife	Space heater	12.5%	++	0	0	0
27. J.H.	Farmer	Diesel tractor, short stack	15%	+	+	+	0
28. C.L.	Farmer	Diesel tractor	10%	+	0	0	0
29. E.S.	Elderly housewife	Space heater	21%	+	0	0	+
30. J.R.	Farmer	Diesel tractor	17%	+	0	+	0

TABLE I.—CASES OF CHRONIC CO ASPHYXIA, SWIFT CURRENT, SASKATCHEWAN, 1954 - 1957

Case 1956	Occupation	Source of CO	COHb	Headache	Anorexia, nausea	Weakness	Dizziness
31. E.K.	Saleslady (Convalescent from hepatitis. Acute CO poisoning).	Gas engine lawn mower operated in bargain basement during repairs, 1 hour.	15%	+	+	0	0
32. C.T.	Salesgirl	Space heater in bedroom	12.5%	+	0	0	0
33. B.K.	Salesgirl	Hole in car exhaust muffler	12.5%	0	0	+	+
34. H.E.	Housewife	Gas-heater type of iron	15%	++	++	+	0
35. M.B.	Housewife	Converted wood stove to gas; bad chimney connection	11%	+	0	+	0
36. J.M.	Garage worker	Car exhaust	12%	+	0	0	0
37. E.G.	Housewife (elderly)	Space heater	17%	+	0	+	+
38. H.R.	Farmer	Diesel tractor	12%	+	0	0	+
1957 39. Mrs. T.K.	Hotel cleaner	Works on top floor—fumes from furnace room via laundry chute? CO tests on top floor neg.	20% Anæmia (Hb. 55%)	+	+	+	0
40. T.K.	Bartender	Control	none	0	0	0	0
41. H.R.	Farmer	Diesel tractor	12%	+	0	0	0
42. P.P.G.	Truck driver	New truck; 0.05% CO at heater inflow to cab	25%	+	+	0	+
43. Mrs. P.P.G.	Housewife	Control	none	0	0	0	0
44. J.T.	Truck driver	Same truck as in case No. 42	24%	+	+	0	0

18%. . . . In five cases the COHb content was greater than 14%. Three of these showed 19.7, 21.1, 30.1%, well beyond any normal limits."

CONCLUSIONS

In spite of careful history-taking the author was often unable to make a correct diagnosis before the COHb determination.

In cases with a convincing clinical picture and a potential source of carbon monoxide the COHb concentration was normal. In other instances in which a COHb test was almost an afterthought the results showed toxic levels. A review of the history would then reveal the source.

In our series symptoms usually occurred when the blood concentration of COHb exceeded 10%, although certain patients had no complaints at even higher levels.

Our experience during the past three years indicates that illness arising out of chronic exposure to CO is by no means rare, and in certain occupations and environments CO asphyxia precedes "neurosis" or "duodenal ulcer" in the differential diagnosis of headache or dyspepsia syndromes.

SUMMARY

Forty-one cases of chronic CO poisoning were reviewed. Presenting symptoms are headache, anorexia, dyspepsia, weakness and dizziness, singly or in combination. The finding of a COHb level of 10% or more plus the relief of symptoms when the patient is removed from exposure confirms the diagnosis.

All provincial laboratories are equipped to do COHb tests.

The outdoor worker and the housewife are not immune.

Compensation boards will now accept claims for illness arising out of exposure to CO on the job.

Acknowledgment is due Morris Katz, Ph.D., who first brought this problem to the author's attention; Dr. Z. B. Claman, F.R.C.S.(Edin.), for his encouragement and enthusiastic support of this investigation and for his assistance during the preparation of this paper; and the Department of Public Health, Swift Current, Sask., for kindly providing the author with the results of their excellent survey and for their cooperation.

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RÉSUMÉ

L'auteur de cet article s'est intéressé à l'intoxication chronique par l'oxyde de carbone et en a relevé 41 cas. D'après lui il y a intoxication chronique si le taux d'oxycarbonémie est de 10% ou plus, si le malade accuse des maux de tête, de l'anorexie, de la dyspepsie, de la faiblesse et des étourdissements, et enfin, si les symptômes disparaissent de quatre à sept jours après la cessation de l'exposition à la source d'oxyde de carbone et l'inhalation d'un mélange de CO^2 pendant une heure par jour. A la disparition des symptômes, le taux d'oxycarbonémie doit être abaissé à moins de 10%. Les malades de la présente série étaient répartis pour la plupart en trois groupes, à savoir, des employés de garage, des chauffeurs de véhicules (camions, tracteurs, etc.), et des ménagères. Au Canada tous les laboratoires provinciaux d'hygiène sont équipés pour faire le dépistage de l'oxyde de carbone et sa recherche dans le sang. Les commissions des accidents du travail reconnaissent maintenant l'incapacité que cause l'exposition à ce gaz délétère.

PHENOXYMETHYL PENICILLIN (PENICILLIN V) IN THE TREATMENT OF STREPTOCOCCAL TONSILLITIS*

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IT HAS BEEN ESTIMATED that during the last war the equivalent of more than one division was absent from duty each day in the United States Army because of the common respiratory infections.[1] A similar high incidence obtains in civil practice where colds and sore throats form a large proportion of all cases seen.

The part played by the hæmolytic streptococcus varies. In a study in American families over three years, only 5% of the upper respiratory morbidity at all ages was due to tonsillitis and septic sore throat,[2] while two earlier investigations of a similar type gave an even lower figure.[3, 4] Conditions in military practice differ in that the subject is exposed to communal life rather than life in the home unit, with greater opportunities for cross-infection. This is particularly so in recruit formations where "unsalted" personnel meet mass infection for the first time.

A clinical diagnosis of streptococcal tonsillitis is frequently not confirmed on culture, and previous experience here showed that clinical impressions were disproved in two out of three cases.[5] In a recent investigation in general practice,[6] slightly less than half the expected number gave a positive culture, while Brumfitt and Slater[7] experienced the same difficulty with a group of army patients.

Apart from the immediate effects and suppurative complications of streptococcal infection, its importance lies in its ability to cause rheumatic fever and nephritis in a small proportion of cases. According to American authorities the former follows untreated or inadequately treated group A streptococcal infections in about 3%.[8] This has been repeatedly confirmed in America by the work of the Streptococcal Diseases Laboratory under Rammelkamp and by Seal of the U.S. Navy with Medical Research Unit No. 4. The work of these groups was directed to the control of epidemic streptococcal infection by antibiotic prophylaxis in young military personnel.

The incidence in Britain is thought to be below 1%,[7,9] although Bywaters[9] thought that it might rise to as high as 10% during epidemics, presumably due to single virulent types.

It was formerly held that the development of rheumatic fever was linked to a high antibody response which could be inhibited by early penicillin; but by delaying treatment, Catanzaro and his group[10] showed that rheumatic fever could be prevented while antibody response was uninhibited. They postulated that the presence of the streptococcus is necessary for a rheumatic manifestation. In the years immediately following the initial attack the subject is particularly liable to subsequent rheumatic episodes. Without continuous streptococcal prophylaxis this has been reported as high as 85%.[11]

During the past six years 54 cases of rheumatic fever were admitted to this hospital from a population of 27,228, average strength; 42 were first and 12 second or subsequent attacks. Only one case could be traced to the ward for upper respiratory infections, and this man had been discharged six weeks before although still harbouring streptococci in his throat.

Nephritis as a sequel of streptococcal infection is variable, as only a few types are strongly nephritogenic, type 12 being the main example.[8] It is therefore likely to follow in single, nephritogenic-type epidemics, as was the case in the small school outbreak reported by Siegel and his colleagues.[12]

Apart from specialized groups, there has been a decline in the incidence of rheumatic fever in parallel with a decline in the frequency and severity of streptococcal diseases generally.[13]

Group A streptococci are universally sensitive to penicillin, and this is the antibiotic of choice except in patients with known penicillin sensitivity. The size of the daily dose is not so important as the duration of treatment, and the American Heart Association recommends that a detectable plasma level should be maintained for 10 days.[14] With 800,000 units daily by injection for four days Brumfitt and Slater[7] found the carrier rate at one month unchanged as compared to a control group. The duration of treatment covered the period of clinical cure. Using a slightly smaller dose for five

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days Denny and his group [15] found a carrier rate of 10% after three weeks while Ström[16] with a six-day course, mainly in children, had a follow-up rate of 6.4%.

Phenoxymethyl penicillin.—The stability of phenoxymethyl penicillin (penicillin V) in acid medium was first demonstrated in Austria,[17] and after its success on the Continent it was re-introduced in America and made generally available there late in 1955.[18] By ingestion it gives a higher and more sustained blood level than oral penicillin G although peak concentration is slightly later.[19] As with all oral penicillins absorption varies from individual to individual but it may be said that if oral penicillin G is one-fifth to one-quarter available, about one-third to one-half the oral dose of penicillin V is therapeutically active. Bowel upset may follow its use in some cases but Quinn and his colleagues[20] have used two mega units four-hourly for six weeks in four cases without untoward effects.

Present investigation.—Five hundred and fifty cases of upper respiratory infection were seen during January to December 1956: tonsillitis 315; pharyngitis 33; quinsy 31; and common cold 171. In the last category were several cases of primary atypical pneumonia, influenza A and C and adenovirus infection, diagnosed retrospectively on paired sera. One hundred and ninety-five cases were considered to be streptococcal in that they had a predominant growth of beta hæmolytic streptococci by throat swab culture associated with localizing symptoms in the throat: tonsillitis 176; pharyngitis 13; and quinsy six. The streptococcus was of group A in 160, group C in 18 and group G in 17. Five cases of throat infection with a group A positive strain and a history of penicillin sensitivity are not included. Only one case of scarlet fever was notified during the year.

Procedure.—All cases were admitted to a cubicled ward, and throat and nose swabs taken by the admitting physician. These were repeated the following morning. Positive cases were transferred to the open ward for respiratory infections after one day on penicillin V, as were negative cases on the result of the second swab. During treatment 109 positive cases were swabbed daily and all cases were swabbed on discharge after a minimum of one day without treatment. As many as possible were again seen three weeks after discharge, and some persistent carriers were followed up monthly.

Laboratory technique.—Aerobic culture on horse blood, nutrient agar plates was used as a routine. Hæmolytic colonies were subcultured after overnight incubation and doubtful ones grown for a further 24 hours anaerobically. All throat swabs were examined for *C. diphtheriæ* on Hoyle's medium. Group A streptococci were identified by the bacitracin disc method[21] and other groups by Lancefield's acid extraction technique. Penicillin V serum assays were carried out by the method of the Distillers Company (Biochemicals) Ltd., using triplicate plates for each dilution and *Sarcina lutea* as the test organism. Difco streptolysin O reagent was used for antistreptolysin estimations.

Treatment.—Course A: 107 positive throats were treated with 2 to 7.2 mega units over two to four days. Course B: 39 were treated with from 7.2 to 9.4 mega units over five to six days. Course C: 44 with from 9.4 to 12 mega units over eight to 10 days. Penicillin V was given in soluble capsules each containing approximately 200,000 units. Treatment was spread throughout the day, and a night dose was omitted.

Results.—In the cases swabbed daily the carrier rate dropped to 20% by the second day and to 4% by the third day. With extended courses this was negative by the fourth day. After course A, 34 (32%) were positive on discharge with the original type and three had a different type because of cross-infection. One month later 24 were seen and 11 were still found positive. Out of 23 with a negative swab on discharge, three had a positive culture with the original organism a month later. After course B, three (7%) had a culture on discharge positive for the infecting type and a further three were cross-infected. Of the 24 cases with a negative swab on discharge two showed the original type one month later. In course C, all were negative on discharge, apart from a single case of cross-infection; out of 34 followed up the original type reappeared in three.

Antistreptolysin O.—A three-tube rise or over was regarded as highly significant. The results are given in Table I.

TABLE I.—RESULTS OF ANTISTREPTOLYSIN TITRATIONS

	No. of tests	*No. Neg.*	*3 tube rise*	*4 tube rise*	*5 tube rise*	*6 tube rise*
Course (1)	14	12		1		1
Course (2)	12	8	1	1	2	
Course (3)	33	29	3	1		

Of the 10 positive cases four were carriers on discharge or at follow-up and two had become cross-infected.

Serum assays.—Twelve serial estimations were carried out with the dosage employed. The highest concentration reached was 2.5 μg./ml. and one case did not show a detectable level at any time. The results showed great individual variation.

Side-effects.—In all, 336 cases were treated with penicillin V and 39 (11.5%) showed some intolerance. The main complaint was of abdominal cramping and bowel looseness coming on about the third day and usually subsiding by the fifth day, but in some, symptoms persisted throughout the course. Treatment was stopped on two occasions because of vomiting, and an urticarial reaction was twice seen. A few complained of pruritus ani but this was trivial as compared to tetracycline irritation.

Sequelæ.—No case of rheumatic fever appeared among those treated in the ward for upper respiratory infection during the study period, and one

patient with a sore throat (type 12 streptococcus) and nephritis was admitted as such.

Discussion.—The beta hæmolytic streptococcus is only one among several causes of tonsillitis. This statement holds good for the expected winter outbreaks in open communities, but in a semi-closed group, the introduction of a virulent type will cause a rapid spread and the chances of a positive diagnosis on clinical grounds are considerably increased. The outbreaks in U.S. naval recruit camps during the winter 1954-55[22] were chiefly due to two virulent types; the "resident" types do not possess this explosive invasiveness. No predominant types were met with here during 1956.

Considerable emphasis has been placed on the method of swab taking. Although the admission swab here was taken in a variety of ways, the following morning several hours after the last local medication and before initiating specific treatment swabbing of the fauces, tonsils and posterior pharyngeal wall was meticulously carried out, using a face shield and forehead lamp. In 30 (15%) of the 195 positive cases, the second swab showed a heavy growth of streptococci with a negative first swab.

Practically all patients with sore throats nowadays will receive some form of antibiotic therapy, usually penicillin. In streptococcal cases this should be continued for 10 days, and without bacteriological facilities an extended course should be aimed at. Treatment will thus be continued well past the period of clinical cure, with considerable administrative difficulties and antagonism on the part of the patient. Course C is quite impractical in hospital as bed space would be rapidly blocked during epidemics, but in small closed groups this would be administratively simple, as supervised treatment could be continued on an ambulant basis after apparent cure. In a home-treatment study from Boston using oral penicillin G over a seven-day course,[23] about one-third of the patients defaulted because they felt well and forgot to take the tablets; an even higher percentage could be expected in a young adult population entrusted with self-treatment.

The dosage given here is probably too large in view of the success of benzathine penicillin with its prolonged low serum level. With a total of six mega units over 10 days, about 200,000 to 300,000 units would be therapeutically available each day. On this the incidence of bowel upset should be reduced.

The carrier state tended to clear spontaneously in the second month, but one heavy carrier had 30 mega units of penicillin V in four courses without effect and the tonsils were finally removed with the desired result. The convalescent carrier has hitherto been looked on as fairly harmless, and many patients in this survey were returned to their units with streptococci in their throats without producing localized outbreaks; however, one type 3 carrier infected his wife and child and another infected her family. The position of the schoolchild carrier has been discussed by Jameson,[24] but simple penicillin regimens are available to clear most throats or at least to effect continuous suppression.

Three cases after course C were not cleared of streptococci, two with an eight-day and one with a 10-day period of treatment. In the latter the antigenic response was not inhibited.

Although the numbers in the higher dosage groups are small, the results would seem inferior to those with benzathine penicillin, where eradication of the streptococcus has been claimed in 99%.[25]

SUMMARY

An analysis of upper respiratory infections admitted to hospital from a young adult population over a period of 12 months is given.

A series of 190 streptococcal throats were treated with penicillin V in three courses. The carrier rate fell as the period of treatment was extended. Side-effects are described.

The advantages and drawbacks of penicillin V are stated.

The position of the convalescent carrier is discussed.

I am indebted to the Medical Director General of the Navy for permission to publish. Dr. R. E. O. Williams of the Streptococcal Reference Laboratory, Colindale, London, kindly undertook the streptococcal typing and checked doubtful groups. Eli Lilly & Co. Ltd. generously supplied the penicillin V pulvules used throughout.

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RÉSUMÉ

Certaines enquêtes ont démontré que les amygdalites et les angines à streptocoque n'étaient responsables que de 5% de la morbidité affectant les voies respiratoires supérieures. Des chiffres plus élevés s'appliquent à la vie en groupe comme celle que l'on mène dans les forces armées. Le diagnostic clinique est déroutant en ce que les deux tiers des cas suspects ne peuvent être confirmés par les cultures bactériologiques. La relation pathogénique entre le streptocoque et la néphrite hémorragique aiguë ou le rhumatisme articulaire aigu en fait néanmoins un problème théra-

peutique important. En vue de la susceptibilité du streptocoque du groupe A à la pénicilline, l'auteur entreprit de traiter tous ses cas d'infection respiratoire à streptocoque avec de la pénicilline phénoxyméthyl, produit stable en milieu acide et se prêtant ainsi à l'administration buccale. Un total de 195 cas d'angine à streptocoque furent traités par des doses variant de deux millions d'unités en deux jours à douze millions d'unités en dix jours. Les résultats confirmèrent l'opinion voulant que la durée du traitement compte plus que la dose. En effet, après deux jours de traitement le nombre des porteurs était réduit à 20%, et à 4% le troisième jour. Tous ceux qui furent traités pendant quatre jours et plus ne portaient plus de streptocoque dans leur pharynx. Cependant, le microbe réapparût par la suite chez certains d'entre ceux-ci. On nota de l'intolérance au traitement chez 11.5% des cas; elle se manifesta sous la forme de crampes abdominales, de diarrhée, de vomissements et d'urticaire.

TRAUMATIC RUPTURE OF THE SPLEEN: REPORT OF 11 CASES

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THIS REPORT of 11 cases of rupture of the spleen from 1949 to 1956 is offered for addition to the literature, firstly because of the increase in the number of this type of injury, and secondly because of the gratifying results attained when the possibility of such an injury is kept in mind during the examination of injured persons.

INCIDENCE

There is no doubt that the incidence of rupture of the spleen is increasing. Blain reports 500 cases up to 1925, and over 1000 cases by 1950. Some authors[1-5, 7] find that this increase parallels closely the rise in automobile and industrial accidents. Byrne[5] reports 101 cases of splenic rupture with a history of trauma, in which 50 persons were involved in automobile accidents; 25 of these were passengers and 25 pedestrians. Mansfield,[6] in his series of 16 cases of splenic rupture, reports only three cases due to automobile injuries, the remainder being due to falls or blows upon the abdomen.

In our series of 11 cases of splenic rupture, six cases were the result of automobile accidents and five were due to falls or blows.

The age distribution follows closely that reported in the literature. We found that three cases occurred in persons aged 32, 43, and 36 years, and the remaining eight cases in persons under the age of 21 years.

Table I shows the age and sex of patients, and method of injury.

TYPE OF ACCIDENT AND ASSOCIATED INJURIES

The manner in which a person sustains a rupture of the spleen, in cases not involved in automobile accidents, can usually be obtained from the history without much difficulty, especially in acute cases. However, delayed splenic hæmorrhage may require diligent investigation into its cause.

A history of a fall or blow upon the abdomen is commonly elicited, and the force of such a blow may be moderate in degree. It is not uncommon for such a blow or fall to be forgotten entirely. One of our patients, an 18-year-old male, was admitted to hospital complaining of generalized abdominal pain accompanied by nausea and two bouts of vomiting. The abdominal pain later became localized in the right lower quadrant (RLQ), with tenderness on palpation. This patient was seen in consultation and appendicitis was diagnosed. A McBurney's incision revealed free blood in the peritoneal cavity; a left transverse subcostal incision was then made and splenectomy performed. On subsequent investigation the patient recalled being struck in the abdomen while playing ball.

TABLE I.—AGE AND SEX OF PATIENTS AND METHOD OF INJURY

Age	*Sex*	*Method of injury*
4	M	Fall—9 ft. to the ground.
5½	M	Fall—striking abdomen against boulder.
8	F	Struck—by automobile.
11	F	Fall—4 steps, striking abdomen.
12	M	Fall—from bicycle.
16	F	Car accident.
18	M	Blow—upon the abdomen by ball.
21	M	Car accident.
32	M	Car accident.
36	F	Car accident.
43	M	Car-train accident.

Nigro and Buskirk[8] report a case in which a ruptured spleen was found after a diagnosis of ectopic pregnancy had been made and operation carried out. Kobak *et al.*[9] also report a similar diagnostic problem. Ward[11] reviews the incidence, theories and problems of spontaneous rupture of the spleen, whose existence many authors deny.

Persons involved in car accidents present a serious problem. Multiple injuries such as fractures, head injuries, a hæmothorax or pneumothorax, and lacerations, of which a person may sustain one or more, occur very commonly and may be associated with unconsciousness. The physician should always be especially mindful of abdominal injuries, particularly that of rupture of the spleen.

Delayed hæmorrhage is to be feared and watched for; a 32-year-old male, who had been involved in a car accident and was being treated in hospital

for fractures, suddenly on the eighth day after injury became pale and clammy with evidence of severe shock. He complained of pain in the epigastrium. Immediate treatment by transfusion and operation revealed a rupture of the spleen. Old dark clots were present in the abdominal cavity and in portions of the spleen.

Byrne[5] notes the almost total absence of case reports of splenic rupture in sports injuries, but Bollinger and Fowler[7] recorded two cases due to football injuries in their series of 24 cases.

As mentioned before, the presence of associated injuries may to some degree cause the examiner to overlook the possibility of intra-abdominal hæmorrhage.

Larghero Ybarz and Giuria[10] report that fracture of the ribs is most important because of its frequency and significance in arriving at a diagnosis. Fracture of the ribs occurs in adults and is not usually found in children. The greatest number of cases of splenic rupture is, however, found in the younger age group.

Table II outlines the associated injuries reported by Blain,[1] and those present in the 11 cases in our series.

TABLE II.—SPLENIC RUPTURE AND ASSOCIATED INJURIES

Type of associated injury	*Roettig, Nusbaum and Curtis*	*Wright and Prigott*	*Blain Clinic*	*A. and D. Gaum*
Fractured ribs	5	10	3	1
Hæmopneumothorax	3	4	1	2
Fractures, excluding ribs and skull	3	8	0	2
Contusion of pancreas	1	0	0	0
Injured kidney	2	6	0	0
Retroperitoneal hæmorrhage	1	0	0	0
Ruptured liver	2	3	0	0
Skull fracture	0	5	0	1
Ruptured diaphragm	0		0	1
Ruptured bladder	0		0	0
No associated injury	5	0	4	7

Delayed rupture of the spleen is of great importance. The interval between injury and the appearance of signs and symptoms of intra-abdominal hæmorrhage varies between less than one hour and upwards of 14 days. Mansfield[6] states that it may run as high as several months. The literature reports several cases operated upon 14 days after the trauma.

Various factors are observed which may influence the time of hæmorrhage into the abdominal cavity from a ruptured spleen. Subcapsular hæmorrhage may be present for several days before rupture of the capsule takes place. Small lacerations may undergo a tamponade in the form of a clot, omentum or bowel. The state of shock may prevent hæmorrhage for hours in some cases of ruptured spleen.

Mention is made of patients displaying a typical period of delayed hæmorrhage from a splenic rupture; Byrne[5] reports 13 in his series of 101 cases. Bollinger and Fowler estimate, from the literature reports of 258 cases of ruptured spleen, that 21.5% were of the delayed type. They also present a detailed study of the clinical picture under the following headings: (1) evidence of loss of circulation, blood volume; (2) evidence of a mass; (3) evidence of peritoneal irritation; (4) basal pleuritis.

In our series of 11 cases, we have had two cases of true delayed rupture of the spleen, one which occurred eight days after a car accident and one nine days after a blow in the abdomen by a hard ball. These cases have already been mentioned. In the remainder of our series, nine cases, the lapse of time from trauma to operation did not exceed 26 hours. Table III illustrates our findings.

TABLE III.—LAPSE OF TIME FROM TRAUMA TO ONSET OF ILLNESS AND TO OPERATION

Method of injury	*Time from injury to onset of illness*	*Time from injury to operation*
1. Automobile accident	immediate	14 hours
2. Fall—9 ft. to ground	immediate	6 hours
3. Fall—down 4 steps	immediate	8 hours
4. Fall—from bicycle	4 hours	26 hours
5. Automobile accident	immediate	23 hours
6. Train-car collision	immediate	7 hours
7. Fall striking abdomen on boulder	7 hours	18 hours
8. Blow to abdomen	8½ days	9 days
9. Automobile accident	immediate	5 hours
10. Automobile accident	immediate	8 days
11. Automobile accident	immediate	12 hours

SYMPTOMS, SIGNS AND LABORATORY AIDS

These are well reviewed by Mansfield.[6] He summarizes the diagnostic findings in cases in which the history reveals the possibility of splenic rupture. They are of such importance that it was thought worth mentioning them again.

1. Listlessness and pallor (aside from this, patients appear well).

2. Moderate generalized abdominal pain, associated with left shoulder pain (Kehr's sign). This sign may be produced or aggravated by deep pressure in the left hypochondrium.

3. Left chest pain on deep inspiration.

4. Tenderness to rectal palpation.

5. Slight elevation of temperature or more often of pulse rate.

6. Shock (may or may not be present).

7. Laboratory aids:

(a) Red cell count (R.B.C.) depressed and hæmoglobin values in proportion to the R.B.C.

(b) White cell count elevated, with increase in neutrophils.

(c) Radiographs of the abdomen may show significant findings.

As mentioned, the symptoms or signs may be masked by more obvious injuries, but when the possibility of intra-abdominal injury or hæmorrhage is kept in mind the physical and laboratory signs

of splenic rupture if elicited may be of great benefit. Difficulty in diagnosis is greater if tamponade or subcapsular hæmorrhage is present from the time of injury. Some authors advise abdominal paracentesis, but in some cases negative results are not conclusive.

The findings in our series of 11 cases are outlined in Tables IV and V.

TABLE IV.—SYMPTOMS ON ADMISSION AND METHOD OF INJURY

Age	*Method of injury*	*Symptoms*
8	Struck by automobile	General abdominal pain, marked in left upper quadrant; pain left thigh; pain in calvarium.
5½	Fell, striking abdomen against boulder	Generalized abdominal pain, nausea and vomiting.
12	Fell from bicycle	Sudden severe upper abdominal pain followed by unconsciousness.
4	Fell 9 feet	Upper abdominal pain for previous 24 hours localizing in left upper quadrant.
21	Automobile accident	Upper abdominal pain; pain due to head laceration.
43	Train-car collision	Comatose.
11	Fell down 4 steps	Pain in left upper abdomen; pain in left shoulder.
16	Automobile accident	Generalized abdominal pain.
18	No history	Generalized abdominal pain with nausea, later localized in right lower quadrant.
36	Automobile accident	Unconsciousness.
32	Automobile accident	Sudden abdominal pain 8 days later, with pain in left shoulder.

The radiographic findings in this series have been disappointing. Mansfield[6] reports that by themselves radiological findings are not pathognomonic. Blain[1] states that there are four cardinal signs to be searched for in a flat plate of the abdomen: (1) elevation of the left diaphragm; (2) decreased density in the left upper quadrant; (3) displacement of stomach towards the right; (4) free fluid between the loops of intestine.

of the properitoneal fat line extending up the lateral wall.

It is quite possible that x-ray plates of the abdomen taken soon after an injury would be less likely to show lesions of the spleen than if they were taken 24 hours later. It is thus deemed advisable to repeat this diagnostic procedure when diagnosis of intra-abdominal injury or hæmorrhage is difficult or suspected.

Larghero Ybarz of Montevideo (1941) described the four signs shown in Fig. 1: (1) raised left hemi-diaphragm; (2) displacement of the gastric shadow towards the midline; (3) subphrenic opacity; (4) descent of the left part of the transverse colon.

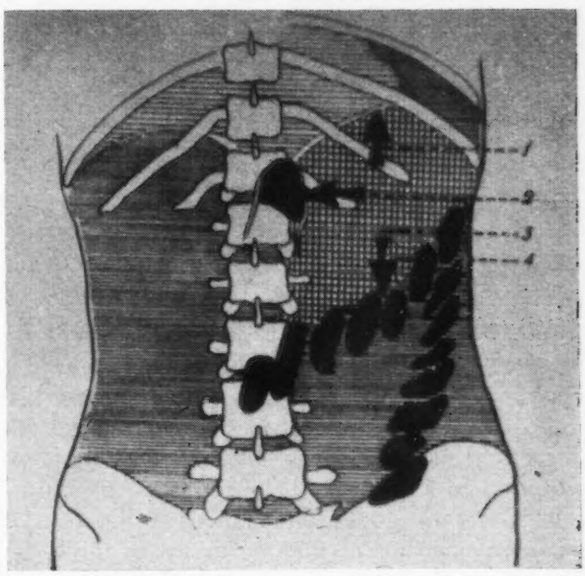

Fig. 1.—Schematic drawing of the roentgen syndrome in rupture of the spleen. The four signs are (1) raised left hemi-diaphragm, (2) displacement of the gastric shadow toward the median line, (3) subphrenic opacity, (4) descent of the left part of the transverse colon. (From *El Estudiante Libre* by P. Larghero Ybarz, Montevideo, 1941. By permission of *Surgery, Gynecology and Obstetrics.*)

TABLE V.—PHYSICAL EXAMINATION AND LABORATORY AIDS

Patient age	*Pallor*	*Clinical shock*	*Abdominal tenderness*	*Localized tenderness*	*Abdominal rigidity*	*Temp.*	*Pulse*	*B.P.*	*Hb.%*	*R.B.C.*	*W.B.C.*
8	2-plus	2-plus	Left side	Left side	Left 1-plus		116	100/30 mm.Hg.	40		
5½	2-plus	2-plus	Generalized	LUQ	2-plus		100		48	3,950,000	18,900
12	1-plus	2-plus	Epigastric	LUQ	2-plus		110	90/30	70		
4	1-plus	0	Epigastric	LUQ	Left 2-plus	100° F.	120		64		
21	1-plus	1-plus	Epigastric	LUQ					85	4,130,000	18,000
43	3-plus	4-plus	Generalized	LUQ	3-plus		140	60/40	66		
11	2-plus	0	Epigastric	LUQ	1-plus	99.6° F.	130		80		15,000
16	2-plus	2-plus	Generalized	LUQ	2-plus		100		63	3,240,000	25,000
36	3-plus	4-plus	Generalized	None	3-plus		118	50/20	71		
32	3-plus	3-plus	Generalized	Left	2-plus		116		62		

In our series of ruptured spleen cases, a flat plate of the abdomen was taken in addition to radiographs of chest and other sites of injury, with the exception of one patient in whom the clinical symptoms pointed strongly to appendicitis. Only in one case were there findings of pathological significance: the abdomen showed a slightly increased density in the left side, with obliteration

PATHOLOGY OF SPLENIC RUPTURE

In this series of 11 cases, operation revealed free blood in the abdominal cavity of 10 patients. In one patient, with delayed hæmorrhage, old dark clots were present, indicating tamponade. In the other case of delayed hæmorrhage, the pathologist's description of the spleen indicated a subcapsular hæmorrhage which had finally burst the

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TABLE VI.—SURGICAL PATHOLOGY

Age	*Type of injury*	*Gross pathology*
8	Struck by car	Stellate rupture convex surface; multiple tears in pulp substance.
5½	Fall, striking abdomen on boulder	Severe laceration near hilus; small laceration on inferior border.
12	Fall from bicycle	Spleen torn in two.
4	Fall—9 feet	Large irregular tear anterior border; micro - hæmorrhage over large area with destruction of substance.
21	Automobile accident	Subcapsular hæmorrhagic laceration.
43	Train-car collision	
11	Fall—4 steps	Extensive laceration from upper border into hilus.
16	Automobile accident	Extensive hæmorrhage under capsule extending over half of upper surface; two linear tears approximately 6 cm. in length.
18	Struck on abdomen by ball	Superior surface: capsule is split and retracted revealing bare surface covered with extensive hæmorrhage.
36	Automobile accident	Approximately 1/3 of spleen has almost been completely severed from main portion.
32	Automobile accident	

capsule. In all cases, microscopic examination of the spleen revealed normal tissue.

Table VI shows the type of trauma and the gross pathological findings. It is apparent that the method of injury does not influence the degree of trauma to the spleen. The force of the blow in itself is not of great importance. A blow to the abdomen, whether of greater or lesser force, may injure the spleen. It is probable that the greater the force the greater the likelihood of splenic injury. Table VII summarizes the surgical pathology of the spleen.

TABLE VII.—SURGICAL PATHOLOGY

Splenic injury	*No. of cases*
Single laceration	2
Subcapsular hæmorrhage	1
Multiple or stellate lacerations	4
Laceration extending into hilus	2
Bisection	2

Basal pleuritis.—A short time ago we observed a patient with delayed splenic rupture whose chest radiograph three days after injury and just before splenic rupture demonstrated marked left basal pleuritis and associated minimal fracture of the left ninth rib. This basal pleuritic reaction was characterized by moderately increased diffuse density of the left lower lung field, most marked at the diaphragm and gradually disappearing one or two rib spaces cephalad. We thought that this clouding might be the result of the influx of fluid or cells into the diaphragmatic pleura and nearby lung tissue as a local response to the accumulation of blood beneath the diaphragm from a damaged

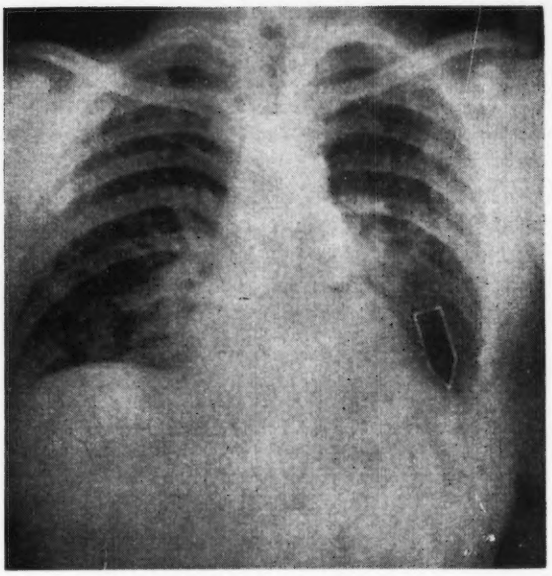

Fig. 2.—Chest x-ray; basal pleuritis without associated rib fracture; splenic rupture occurring two days later.

spleen. We therefore reviewed our other cases of delayed splenic rupture to determine whether or not such a pleuritic response was common. We were surprised to note that, whether or not rib fractures were associated, this response was shown by all of our four patients with delayed splenic rupture who had had chest films taken more than 24 hours after injury (Figs. 2 and 3). Of the four additional cases of delayed splenic rupture subsequently reviewed at the two military institutions, chest radiographs were taken more than 24 hours after injury in only two; of these, one showed a basal pleuritic response. Thus in five out of six cases of delayed splenic rupture in which radiographs were taken 24 hours after injury a basal pleuritis was shown. The incidence of this pleuritic response in fractures of one or more of

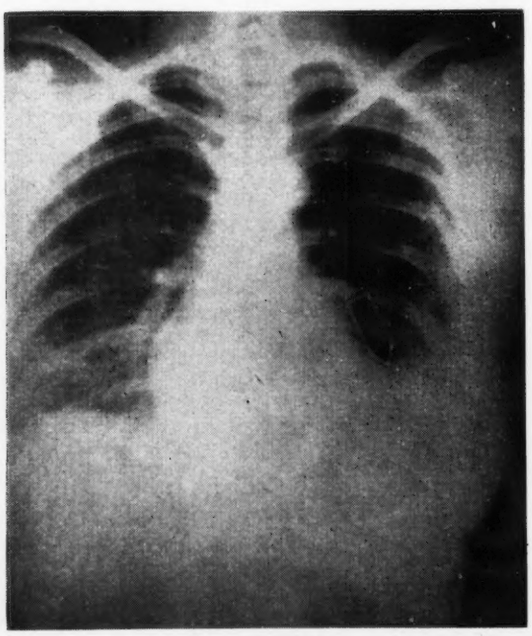

Fig. 3.—Chest x-ray; basal pleuritic reaction with associated rib fractures; delayed splenic rupture occurring four days later.

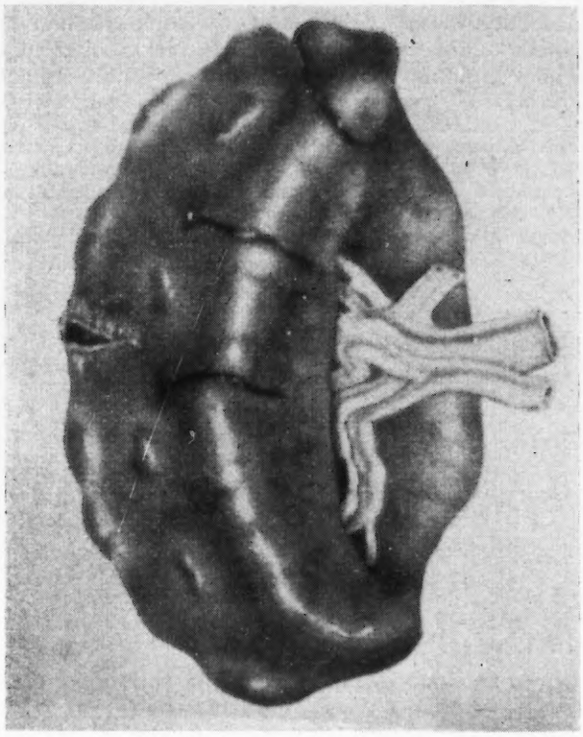

Fig. 4.—McIndoe's first type of splenic rupture.

the five lower left ribs is of interest. Of 126 consecutive cases in which chest films were taken 24 hours or more after injury, such a response was demonstrated in nine. However, of these, four patients were found at operation to have delayed splenic rupture and two, as already mentioned, had findings compatible with splenic injury; in the remaining cases, although splenic rupture may have been present, we were unable to make such a clinical diagnosis. Because of the relative frequency of this basal pleuritic response in cases of delayed splenic rupture, we believe that it is a diagnostic sign of some importance and deserves, if possible, corroboration and emphasis.

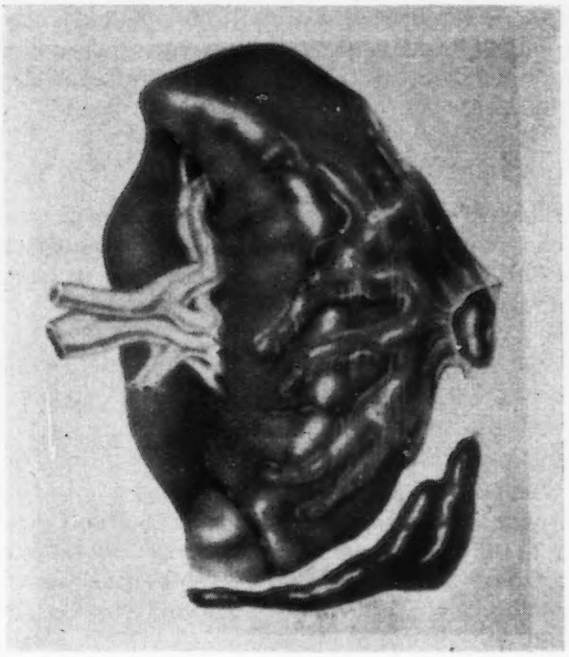

Fig. 6.—McIndoe's third type of splenic rupture.

TYPES OF SPLENIC RUPTURE

Splenic rupture occurs as an isolated injury and also in association with other injuries. In general, there are four main types of rupture in closed injuries: avulsion of the spleen from its vascular pedicle, or complete disruption of the spleen, and the three types of ruptures described by McIndoe: (1) minor superficial capsular rupture or slight splenic contusion producing parenchymal ecchymosis; (2) intrasplenic hæmatoma and subcapsular hæmorrhage without capsular rupture; (3) capsular and parenchymal rupture with perisplenic hæmatoma.

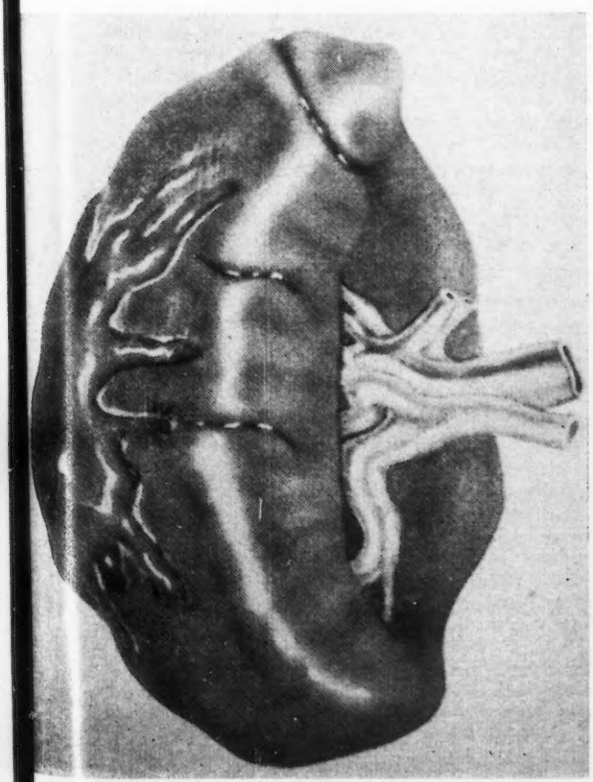

Fig. 5.—McIndoe's second type of splenic rupture.

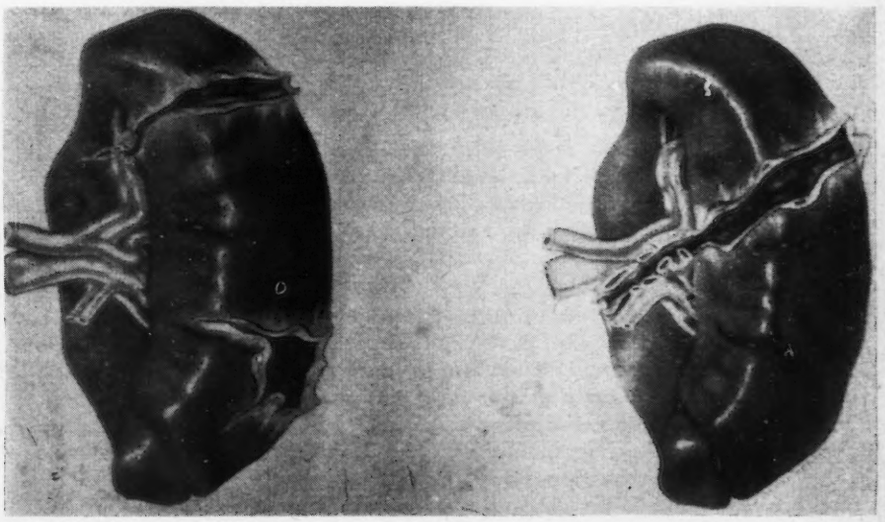

Fig. 7.—Avulsion of the spleen from its pedicle and complete disruption of the spleen.

Avulsion injuries are often rapidly fatal, whereas the other types may produce early or delayed symptoms. Figs. 4, 5, 6 and 7 illustrate the types of rupture.

TREATMENT

The treatment of splenic rupture is splenectomy. Many authors advise laparotomy in suspected cases of splenic rupture, and indeed if suspicion of any intra-abdominal trauma is present.

In the postoperative phase, the degree of shock present is important. The shock must be reduced to a point at which operation may be carried out as soon as possible. The usual methods of combating shock, such as administration of intravenous fluids or plasma expanders, may be used. However, transfusion of whole blood is without equal, and more often than not is essential to maintain life. Byrne[5] states that it is better to transfuse the patient when about to perform splenectomy. Attempts to replenish blood loss and reduce shock without splenectomy may be disastrous or result in a stormy recovery. Transfusion is also advisable in patients not showing any degree of shock, because, although the operation in itself is not a difficult procedure, handling of the spleen before ligation of the splenic vessels may cause sufficient loss of blood to throw the patient into shock and endanger life.

Postoperative recovery is usually uneventful. However, periodic examination should be carried out to guard against complications, the most common of which is basal pleuritis. Aspiration of vomit is also to be watched for in the early hours after operation.

One of our patients, a 5½-year-old boy, stopped breathing and became cyanotic 20 minutes after splenectomy. The child was bronchoscoped and cheesy material aspirated from the bronchi; intravenous nikethamide (Coramine) was also given and the child recovered.

It has been found in our series, and in the literature, that gastric suction during and following operation enhances recovery; it is a highly recommended procedure in all age groups.

In our series of 11 cases of splenic rupture, excluding those with associated injuries, the average period of hospitalization was 12.4 days. No patient died. However, there are many cases of trauma with fatal results in which the ruptured spleen is the immediate cause. Indeed, before the era of ease of transfusion, splenic rupture had taken a heavy toll of life.

SUMMARY

Eleven cases of traumatic rupture of the spleen, two of which were of the delayed hæmorrhagic type, are added to the literature.

An increase in incidence of traumatic rupture of the spleen is apparent. This is due partly to the increase in automobile accidents, and to recognition that such a condition may exist in injured persons.

The importance of a history of trauma in patients complaining of abdominal pain is commented upon.

The symptoms, signs and laboratory aids which are diagnostic of splenic rupture are reviewed.

The authors would like to acknowledge the assistance given them by Dr. J. A. MacLellan in the preparation of this paper, and to thank the Alexander Blain Hospital and Clinic, the *American Journal of Surgery* and Drs. J. A. Bollinger and E. F. Fowler for permission to reproduce illustrations.

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RÉSUMÉ

Six des 11 cas de rupture de la rate rapportés par l'auteur étaient le résultat d'accidents d'automobiles; la majorité des malades étaient âgés de moins de 21 ans. Le diagnostic n'est pas toujours facile à poser car les contusions et fractures multiples des grands blessés peuvent attirer l'attention sur elles-mêmes au détriment de cet organe. De plus, dans les cas d'hémorragie retardée, le traumatisme initial parfois insignifiant est souvent oublié et les symptômes n'apparaissent quelquefois que plusieurs jours sinon plusieurs mois après l'accident. Ce décalage est la cause de diagnostics erronés d'appendicite ou de grossesse tubaire comme on a déjà vus dans certains de ces cas. Les principaux symptômes que présentent un traumatisé de la rate sont des douleurs abdominales, des douleurs à l'épaule gauche et à l'hémithorax gauche à l'inspiration profonde; l'état de choc n'est pas toujours présent. La radiographie peut offrir quelque aide au diagnostic dans les cas douteux, surtout si on la répète 24 heures après le cliché d'admission. A part les cas d'avulsion ou de broiement du viscère, les lésions traumatiques se divisent en rupture superficielle de la capsule, en hématome intra-splénique sous-capsulaire sans rupture dans la capsule, et en déchirement avec hématome périsplénique. La splénectomie d'urgence est le meilleur sinon le seul traitement. Les mesures de réanimation doivent avoir préséance si le malade est en état de choc. Comme l'intervention est souvent sanglante, les transfusions sont indiquées pendant l'opération. L'aspiration gastrique pendant la période per- et post-opératoire est un adjuvant utile.

CARDIORESPIRATORY DYSFUNCTION AND POLYCYTHÆMIA IN PATIENTS WITH EXTREME OBESITY

In patients without primary pulmonary or cardiac disease marked obesity may lead to alveolar hypoventilation, arterial hypoxæmia and hypercapnia, which, in turn, may produce secondary polycythæmia, somnolence, pulmonary hypertension and right heart failure. Adequate loss of weight is accompanied by complete disappearance of this cardiorespiratory syndrome.

In patients with primary pulmonary or cardiac disease, the presence of obesity may aggravate the dysfunction, and loss of weight may effect considerable clinical improvement. It is suggested that the mechanical effects of obesity in increasing the work of breathing is the primary factor in the genesis of the alveolar hypoventilation which appears to be the significant functional abnormality.—G. A. Lillington *et al.*: *Proc. Staff Meet. Mayo Clin.*, 32: 585, 1957.

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Case Reports

FATAL ACUTE HÆMOLYTIC ANÆMIA, THROMBOCYTOPENIC PURPURA, NEPHROSIS AND HEPATITIS RESULTING FROM INGESTION OF A COMPOUND CONTAINING APIOL*

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DONALD H. BALLEW, M.D., *Montreal*

A CONSIDERABLE NUMBER of reports on apiol poisoning are contained in Dutch, German and French literature between 1931 and 1938. Only an occasional case has been reported in the English literature. The reported cases may be placed in three groups:

1. Those in which polyneuritis was the predominant manifestation; in these patients the polyneuritis was shown to be due to a contaminant, triorthocresylphosphate;
2. A few in which the predominant manifestations were due to an extensive encephalopathy; and
3. Those in which the predominant symptoms and signs were due to an acute nephrosis with uræmia and associated hepatic dysfunction.

In the present case, the patient ingested a preparation containing apiol and subsequently developed acute thrombocytopenic purpura, hepatic dysfunction and an extremely severe acute hæmolytic anæmia associated with methæmalbuminæmia, hæmoglobinæmia and hæmoglobinuria. Subsequently, an acute lower nephron nephrosis with oliguria, and then anuria and uræmia, developed. A septic peritonitis and septicæmia had followed an attempt at mechanical abortion and thus further complicated the findings.

A 28-year-old white woman was admitted as an emergency to the Royal Victoria Hospital by helicopter from Ottawa on November 2, 1956. She had been amenorrhœic for three months. Between October 14 and October 28 she had taken approximately 36 tablets of a proprietary preparation named Apergol. Six of the capsules were taken on October 28. A male companion who travelled with her stated that she had been taking this preparation irregularly and intermittently for some time before October 14. On October 28 a douche nozzle was stated to have been passed by the patient into the os externum of the cervix, and this was followed by severe pain, syncope, considerable vaginal bleeding and incontinence of stools. While at work on October 29, she suffered a severe chill followed by a rise of temperature to 104°F. She was admitted to hospital in Ottawa where a tentative diagnosis of septic abortion and pelvic peritonitis was made. On October 30 she remained febrile and became deeply jaundiced and incoherent; her urinary output was 150 ml. and her non-protein nitrogen (N.P.N.) was found to be 120 mg. %. On October 31, she was transferred to the Ottawa General Hospital. Her fluid output was 175 ml. A blood culture on that day was later reported positive for a non-hæmolytic streptococcus which grew in both anaerobic and aerobic culture and which was sensitive to tetracycline and to a combination of penicillin and streptomycin. Her companion stated that between the night of October 28 and the morning of October 30 her skin became a deep brown. On October 31 she was found to have severe anæmia with a platelet count of 80,000 per c.mm. and a prolonged prothrombin time. Her blood pressure was 100/50 mm. Hg. She was anuric from October 31 until her transfer to the Royal Victoria Hospital on November 2. Her plasma bilirubin was found to be 10 mg. %. She developed clinical purpura with a platelet count of 70,000. A blackish-brown pigment of the skin was noted and a similar pigment was found in the blood plasma. During this period therapy consisted of 300 mg. of hydrocortone, 100 mg. of cortisone acetate every 12 hours, about 500 c.c. of packed red cells about 500 ml. of 20% glucose in water with insulin every 24 hours and 500,000 units of crystalline penicillin every three hours.

Because of the persistent anuria she was transferred to the Royal Victoria Hospital for consideration of the use of the artificial kidney. On admission, she was a well-developed, well-nourished, dehydrated white female with blood pressure of 105/65 mm. Hg, pulse rate of 84 and temperature of 98° F. Her skin and scleræ showed a diffuse dark mahogany brown pigmentation and, in addition, the scleræ appeared icteric. She was confused, incoherent and unco-operative and appeared acutely ill. There were numerous petechial, purpuric and ecchymotic areas over the body, especially over the arms and legs, and a number of petechiæ were present in the mouth. The heart and lungs were normal to examination. There was marked tenderness over the right upper quadrant. The liver was enlarged to percussion and was thought to be palpable, although a definite edge could not be felt. Pelvic examination by Dr. George Maughan revealed a soft cervix and an enlargement of the uterus suggestive of a 2½-month gestation. The cranial nerves, reflexes and motor and sensory systems were normal to examination.

On November 2, the day of her admission, hæmatologic findings were as follows: Hb. 8.4 g. %; packed cell volume 23%; red cell count 2,400,000 per c.mm.; mean corpuscular volume 96 microns; mean corpuscular hæmoglobin 35 micromicrograms; mean corpuscular hæmoglobin concentration 37%; reticulocytes 4.4%; sedimentation rate (Wintrobe) 67 mm. in one hour (uncorrected), 25 mm. (corrected); platelets 14,000; bleeding time (Ivy) longer than 15 minutes; clotting time 16 minutes (normal 20 minutes); prothrombin time 16 seconds (normal 12 seconds), prothrombin complex concentration 45%; vascular fragility (Rumpel-Leede) markedly increased; clot retraction severely impaired; serum prothrombin time 19 seconds (normal 30 seconds or more) indicating diminution of prothrombin consumption; normal plasma fibrinogen concentration; the thromboplastin generation test was impaired because of a defect in the patient's platelets (i.e. the thromboplastin generation was corrected when normal platelets were mixed with the patient's serum and barium sulphate plasma, but was not corrected when normal barium sulphate plasma and normal serum were mixed with the patient's platelets). Total leuko-

*From the Hæmatology Service of the Department of Medicine of the Royal Victoria Hospital and McGill University.

cytes were 50,000 per c.mm. with 35% (17,500) stabs, 52% (26,000) mature neutrophils, 3.5% (1750) monocytes, 8.5% (4250) lymphocytes, 1% (500) metamyelocytes. In the differential smears many typical microcytic spherocytes, a few target cells and some red cells containing Howell-Joly bodies were seen. The anæmia was normochromic and normocytic. In the test of mechanical fragility, 16.8% of the red cells hæmolysed (normal 2.5%). In the test of osmotic fragility anisohæmolysis was demonstrated, a small portion showing increased fragility and a larger portion of the red cells showing increased resistance. The plasma hæmoglobin was 40 mg. % (normal 1-4 mg. %). The direct and indirect Coombs tests were negative.

It was noted that the blood plasma and serum had a deep mahogany appearance which could have been due to the presence of methæmalbumin and/or methæmoglobin. The serum was submitted to spectroscopic examination: a dark absorption band was present at 6200 Angström units and a fainter band was present at 5800. The Schumm test showed that addition of ammonium sulphide caused the band at 6200 to disappear and an intense band appeared at 6530. These findings pointed to the presence of methæmalbumin. The L. E. test was performed and was negative. It was felt that these findings were diagnostic of severe acute hæmolytic anæmia and thrombocytopenic purpura.

On the day of admission N.P.N. was 222 mg. %, total protein 6.29 g. % with 4.05 g. % albumin and 2.12 g. % globulin; total bilirubin was 20 mg. % with 15 mg. % direct reacting bilirubin, D/T 75%, cephalin cholesterol flocculation test was +++, thymol turbidity 6.8 units and thymol flocculation test was negative, CO_2 combining power was 14.1 mEq./l., serum chloride 91.7 mEq./l., serum sodium 134.5 mEq./l., serum potassium 4.25 mEq./l., serum calcium 3.58 mEq./l., serum phosphorus 3.14 mEq./l. and a sugar level in a random blood sample was 135 mg. %. Blood volume determination on November 3 (using RISA) showed a total blood volume of 4756 ml. (anticipated normal 3742 ml.), a red cell volume of 960 c.c. (anticipated normal 1569 c.c.), and a plasma volume of 3716 ml. (anticipated normal 2150 ml.).

During the three days in hospital before her death, her output consisted of a few drops of dark brown urine. Her N.P.N. rose to 266 mg. % and serum creatinine to 11.6 mg. %; her CO_2 combining power remained at about admission level. Her serum potassium did not rise above normal limits and her E.C.G. showed no evidence suggestive of hyperkalæmia. Her serum sodium and chloride remained slightly below normal. The brownish pigmentation of her skin and plasma decreased. Her total red cell volume decreased to 819 c.c. Her purpura and thrombocytopenia persisted although she received three transfusions of fresh whole blood taken in siliconed flasks through plastic tubing. The prothrombin complex concentration improved slightly after blood transfusion and intravenous administration of large amounts of vitamin K_1.

Her abdomen became increasingly distended. She developed inspiratory and expiratory coarse subcrepitant rales throughout both lung fields. Her mental confusion changed to semi-coma and then deep coma. The spleen was never palpable. Her blood pressure varied from 110-134/60-80 mm. Hg throughout her hospitalization. Her fluid intake consisted of a total of 3000 ml. intravenously, including the transfusions of 1500 ml. of blood. She received large amounts of procaine and crystalline penicillin mixed with streptomycin, 50 mg. of cortisone acetate daily, and testosterone propionate, 50 mg. i.m. twice a day. Because of increasing pulmonary œdema on November 3, 1050 ml. of whole blood was removed by phlebotomy while at the same time 400 c.c. of packed red cells was administered.

On November 4 the paper electrophoretic pattern of the serum proteins showed albumin 57.7 %, alpha 1 globulin 8.3%, alpha 2 globulin 11%, beta globulin 8.3% and gamma globulin 14.6%. The only abnormality present was a slight increase of alpha globulins.

On the evening of November 4 she developed severe acute pulmonary œdema and died.

Because of the nature of the case it was necessary to turn the body over to the coroner, whose report of the gross findings is summarized below:

Scalp, skull, brain, heart, stomach, intestines and bladder: no gross change. Lungs: fairly marked congestion, œdema with areas of atelectasis in the dependent portions. Abundant thick secretions in the trachea and bronchi mixed with a reddish serous fluid. Kidneys: right, 235 g.; left, 260 g.; large red kidneys with extensive cortical hæmorrhages. Cortices of the same colour as the medulla. Pelves not remarkable. Liver: weight 2625 g.; increased in size, œdematous and of a beige-brown colour. Uterus: showed a multiparous cervix and measured 10 x 7.4 x 4.3 cm. It was widely patent and contained a mucopurulent secretion. The enlarged uterine cavity showed a brownish mucosa which was thickened, ragged and sanguineous. No trace of significant instrumental trauma was found; only the left ovary was present.

Microscopic sections of certain organs were obtained from the coroner and the pathological examination was reported by Dr. Douglas Waugh. The heart was normal. Sections of the liver showed normal over-all architecture but there were multiple small foci of necrosis with an increased amount of brown pigment, probably bile, in liver cells and canaliculi around the central veins. A few hepatic veins showed small numbers of lymphocytes and polymorphonuclear neutrophils in their walls. In the ovary fragments of the corpus luteum showed early hyalinization; a few follicles and small fragments of normal cortical tissue were present. The sections of the uterus contained masses of fibrinopurulent material and no recognizable tissue. The proximal and distal tubules of the kidneys were extensively occluded by a granular heme pigment and there was associated focal degeneration of epithelium. Inflammatory changes were inconspicuous. The findings were those of an unusually severe hæmoglobinuric nephrosis (Fig. 1).

The pathologic diagnosis was acute nephrosis of hæmoglobinuric type (marked); focal necrosis of liver with bile stasis.

DISCUSSION

Apiol has been widely used and is stated to produce symptomatic relief in menstrual disorders such as amenorrhœa, menorrhagia, hypomenorrhagia, metrorrhagia and dysmenorrhœa. Supposedly, it stimulates the uterine musculature and induces pelvic hyperæmia. It is a camphoraceous material derived from parsley and has the formula 1-allyl-2,5-dimethoxy-3,4-methylene-dioxybenzene.

Fig. 1.

There is good evidence to believe that this patient ingested 36 capsules of Apergol over a two-week period preceding the onset of her illness and, probably, she took additional capsules for some time before this. According to the manufacturer, each capsule of Apergol contains 0.3 g. of apiol, 0.008 g. of aloin, 0.065 g. of ergotin, and 0.03 g. of oil of savin and aromatics qs. This formula is identical with that of the preparation ingested by the patient reported in 1938 by Lowenberg.[1] Although the product was prepared by a different manufacturer, his patient ingested only 17 capsules and the clinical manifestations were principally cerebral. He tested his preparation for the presence of triorthocresylphosphate but was unable to confirm its presence. As pointed out by Lowenberg and others, the variable pharmacologic properties of preparations containing apiol may be responsible, at least in part, for the different manifestations of poisoning.

Polyneuritis has been the most commonly reported manifestation of apiol poisoning. It has been shown repeatedly, both experimentally[2] and clinically,[3] that the polyneuritis is due to the presence of triorthocresylphosphate, the substance responsible for the Jamaica ginger polyneuritis which occurred in the United States in 1930.[4–6] This substance is used in apiol preparations because it provides the desired bulk to the capsular contents and because it preserves the appearance and consistency of apiol by preventing its precipitation and by having the same general appearance as yellow apiol. The manufacturer of Apergol does not state in the pamphlet attached to his product whether triorthocresylphosphate is present. At no time did our patient show clinical signs of a polyneuritis.

Administration of apiol to dogs has resulted in toxic damage to the liver, kidneys and heart, as do most volatile oils. A number of European authors have reported nephritis resulting from apiol poisoning.[7, 8] In these patients the symptoms appeared one to eight days after the ingestion of apiol, and were associated with elevation of temperature and pulse, nausea, vomiting and abdominal distress, often with diarrhœa. Erythematous and purpuric eruptions of the skin, gingivitis and œdema of the vulva were not uncommon. At least two authors[7, 8] have noted the brownish pigmentation of the skin and the mahogany or blackish colour of the urine associated with oliguria. One author[7] noted the presence of bilirubin, methæmoglobin and hæmoglobin in the urine; he felt that the renal changes were secondary to these findings.

Except for the above report, the presence and significance of a hæmolytic anæmia does not seem to have been stressed. Our patient had a very severe hæmolytic anæmia associated with a marked thrombocytopenic purpura. This spherocytic anæmia was associated with a marked increase of mechanical and some increase of osmotic fragility; it was not of the auto-immune type. The intense pigmentation of the skin and internal organs and the brown pigment in the urine were probably related to the methæmalbuminæmia which, with the hæmoglobinæmia and hæmoglobinuria, was a manifestation of a very severe hæmolytic process. This intense intravascular hæmolysis resulted in obstruction of the proximal and distal tubules of the kidneys, in the acute nephrosis, the anuria and the uræmia. Many of the clinical and pathological manifestations, and probably the death of the patient, resulted from the severe hæmolytic anæmia. During the patient's stay in the Royal Victoria Hospital she remained afebrile and the clinical findings suggested that any infection present had been localized by previous therapy to the pelvis. It is possible that infection contributed to the hæmolytic anæmia. However, the organism recovered from the blood was not of the type associated with hæmolytic anæmia; evidence of systemic infection was minimal during her stay in the Royal Victoria Hospital, and at autopsy evidence of infection was limited to the uterine cavity. It would seem probable that in many of the reported cases of apiol poisoning with renal involvement there was really a lower nephron nephrosis caused by a similar hæmolytic process.

A few authors have reported death from apiol poisoning as a result of widespread cerebral damage.[1, 10, 11] It is suggested by one author that large doses of the drug cause immediate cerebral damage[11] whereas moderate doses may produce delayed effects upon the peripheral nerves. In the

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instances of cerebral damage it is not clear whether this damage was due to apiol or to the presence of triorthocresylphosphate as a contaminant.

Patients with the nephrotic manifestations may also have central nervous system symptoms and signs, such as confusion, psychosis, convulsions and coma. It is not clear whether these symptoms are due to the associated uræmia or whether they are related to co-existent cerebral damage from the apiol poisoning. Unfortunately, the brain of this patient was not examined microscopically.

It is suggested that poisoning due to compounds containing apiol occurs more frequently than might be anticipated from the number of reports in the English literature. The authors are aware of at least two other cases of such poisoning which have occurred in the Montreal area within the past several years. Preparations containing apiol seem to be used principally in the treatment of amenorrhœa. In view of their potential hazards there would seem to be little or no justification for the continued use of apiol for this purpose.*

SUMMARY AND CONCLUSIONS

A fatal case of severe hæmolytic anæmia, thrombocytopenic purpura, acute lower nephron nephrosis and hepatic dysfunction is reported in a patient who ingested 36 capsules of a compound, each capsule of which contained 0.3 g. of apiol. The patient also suffered from a pelvic peritonitis and probably from septicæmia resulting from septic abortion.

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*The following excerpt is taken from the Transactions of the Ninetieth Annual Meeting of the Canadian Medical Association, held in Edmonton in June 1957.—ED.

"The Committee on Pharmacy had discussed the resolution put forward by the Committee on Maternal Welfare concerning oil of apiol and had reported as follows:

'It is a matter of record that this material has been used as an abortifacient and that illness has resulted not only because of its innate toxicity, but also because of the presence of impurities in it. As far as we are aware, it is not used by the medical profession for any purpose, and its inclusion in any preparation registered under the Patent or Proprietary Medicines Act does not appear to be justified. Its use in preparations marketed under the Food and Drugs Act should also be restricted.

'We are therefore in accord with the sentiments expressed in the resolution, and agree that a recommendation be sent forward to the appropriate Divisions of the Department of National Health and Welfare'." Adopted

ACUTE ERYTHRÆMIC MYELOSIS

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PATIENTS in whom are to be found changes in the peripheral blood, in the bone marrow and in the visceral organs resembling an acute leukæmia but affecting essentially the red cell precursors are rarely encountered. It is therefore considered justifiable to report upon a single case.

The case involved a 57-year-old man admitted to St. Mary's Hospital on January 12, 1955, because of the abrupt onset of severe orthopnœa accompanied by hæmoptysis and melæna. He had experienced progressive weakness with angina of effort in the month before admission. Physical examination showed pallor, engorgement of neck veins, congestion of the lungs, peripheral œdema and cardiomegaly, but otherwise was negative.

There was severe anæmia (hæmoglobin level of 4.8 g.) without characteristic features on the stained smear. Platelets were scanty (about 20,000/c.mm.) There were two late normoblasts per 100 nucleated cells. The white cell count was 4700/c.mm., and a careful differential count, made in retrospect after the marrow had been examined, showed:

Eosinophil polymorphs	< 1%
Neutrophil polymorphs	59
Neutrophil metamyelocytes	2
Neutrophil myelocytes	< 1
Myeloblasts	2
Erythroblasts	4
Undifferentiated "blast" cells	3
Lymphocytes	22
Monocytes	5
Reticulum cells	< 1
Plasma cells	< 1
Unidentifiable	2

Bone marrow was obtained from the sternum, and the specimens were prepared by Davidson's

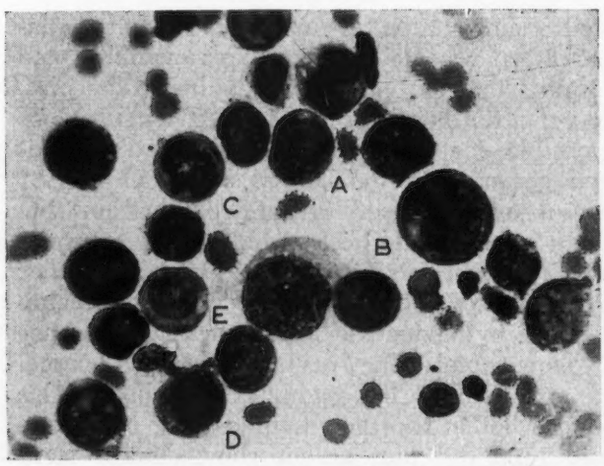

Fig. 1.—Bone marrow smear × 800. A, Erythroblast. B, Binucleate erythroblast. C, Erythroblast in mitosis. D, Megaloblastoid form. E, Large hæmoglobinized cell.

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method[1] and stained by the May-Grünwald-Giemsa technique. The marrow was extremely hypercellular and no fat spaces were evident. Megakaryocytes were rarely to be seen.

The picture was dominated by primitive erythroid cells, recognized as such by the rich blue granular cytoplasm and the finely reticular nucleoplasm. These cells varied greatly in size and some were multinucleated, these being the features which first raised the question of di Guglielmo's disease. In a few cells, reticulation of the nucleoplasm was rather coarse and the appearance was reminiscent of megaloblastic transformation.

Of the later cells in the erythroid series, many were atypical, especially as regards the relative extent of nuclear maturation and of hæmoglobinization. Some were fully hæmoglobinized and yet with a comparatively immature nucleus. Mitotic figures, often abnormal, were seen fairly frequently.

Active phagocytosis by large reticulum cells of normoblasts, less often of erythroblasts, was seen in a number of instances. Myeloid elements were very scarce and, bearing in mind the presence of definite myeloblasts in the peripheral blood, it was surprising to find so few in the marrow.

A differential count on a smear of marrow blood gave the following percentage distribution:

Erythroblasts		70%
Mononuclear	63	
Multinucleated	4	
Megaloblastoid	3	
Normoblasts		9
Early	<1	
Intermediate	2	
Late	2	
Bizarre forms	4	
Neutrophil polymorphonuclears		5
Neutrophil metamyelocytes		<1
Neutrophil myelocytes		2
Neutrophil premyelocytes		<1
Myeloblasts		<1
Eosinophil polymorphonuclears		<1
Eosinophil myelocytes		<1
Basophil polymorphonuclears		nil
Reticulum cells		2
Plasma cells		<1
Lymphocytes		3
Monocytes		nil
Unidentifiable		5

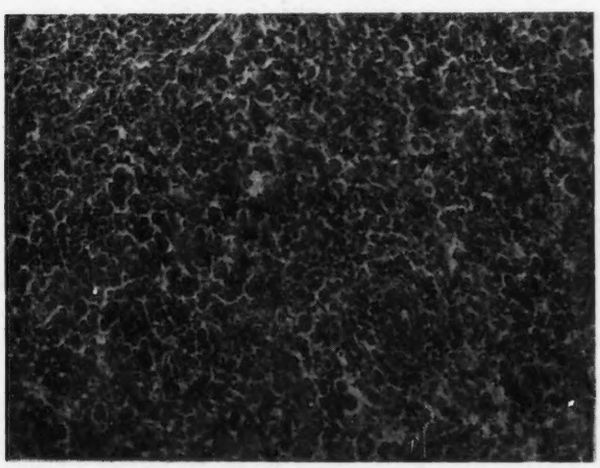

Fig. 2.—Spleen. × 320.

"Smear" cells numbered 27 per 100 intact nucleated cells. It is worthy of note that three of the 42 multinucleated erythroblasts seen in making this count showed an area of sand-coloured fine granulation, like that of a neutrophil, lying between the nucleus and the outer rim of deeply basophilic and coarsely granular cytoplasm.

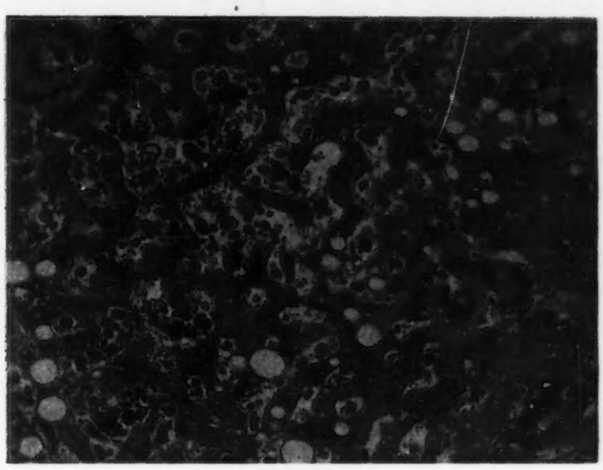

Fig. 3.—Liver. × 320.

The patient was treated as a case of congestive cardiac failure consequent upon profound anæmia.

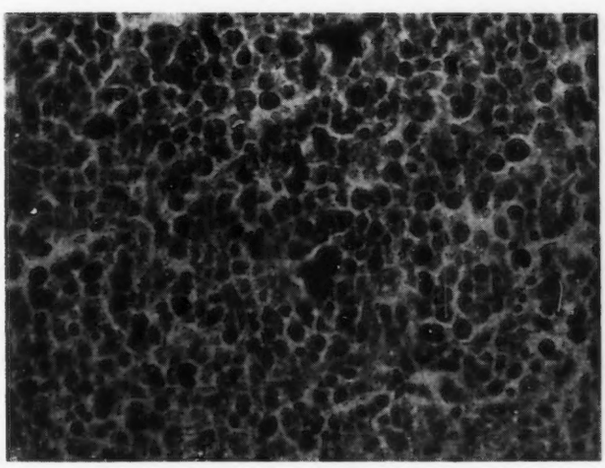

Fig. 4.—Bone marrow section. × 400.

Oxygen, digitalis, diuretics and cyanocobalamin (vitamin B_{12}) were given without appreciable effect on his condition. A cautious transfusion of packed cells was administered on the second hospital day but, despite all these measures, congestive failure progressed and death occurred early on the fourth hospital day.

An autopsy was carried out and showed replacement by primitive erythroid cells of the major portion of the marrow of all bones examined (sternum, vertebræ, ilium and femur) (Fig. 4). There was massive infiltration by similar cells in the spleen (Fig. 2) and in the liver (Fig. 3) which weighed respectively 600 g. and 2800 g. The heart

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was enlarged and dilated. There was marked pulmonary œdema and congestion.

DISCUSSION

The clinical course followed by this case was rapidly downhill to death within a matter of only a few weeks from the onset of symptoms. The hæmatological picture was dominated by primitive red cell precursors and of these many were atypical with gross variation in size, with multinucleate forms and with frequent mitoses, all features suggestive of malignancy.

Finally, the postmortem confirmation of complete marrow replacement and the finding of infiltration in the liver and spleen by primitive cells of the erythroid series put beyond reasonable doubt the suggestion that we were dealing with a process akin to an acute leukæmia, but involving the erythron.

Such a neoplastic proliferation of erythroid precursors had not, according to Pappenheim, been recognized up to 1914. Indeed, it was not until 1917 that di Guglielmo[2, 3] described erythroblastic hyperplasia accompanying what otherwise was an ordinary case of myeloid leukæmia; to this association was given the name of "erythroleukæmia".

In 1923 the same worker described a case, similar to the present one, in which the erythroid elements were affected electively; the process was acute and the condition was termed "acute erythræmic myelosis".

A number of proposed cases have since been published, mostly by European workers, but critical reviews, such as that by Schwartz and Critchlow[4] in 1952, accept as fulfilling all criteria only a minority of the instances cited. Some confusion as to nomenclature has taken place. It would seem perfectly reasonable to use "erythroleukæmia" as the designation when there is abnormal proliferation of both erythroid and myeloid elements, but this term should be avoided when only the erythron is involved. The present title, "acute erythræmic myelosis", proposed by di Guglielmo himself, is clumsy but does possess the advantage of singularity. Possibly, in the future, if polycythæmia vera should become regarded as a chronic neoplastic proliferation of the erythron, then the term "erythræmia" might be used to cover both the acute and the chronic forms of di Guglielmo's disease.

However speculative the relationship might be as between acute erythræmic myelosis and polycythæmia vera, there can be no doubt as to the connection of the former with the leukæmias. This aspect was reviewed most recently by Martin and Bayrd in 1954.[5]

As to the frequency of the type of case which we have presented, Martin and Bayrd cite Moeschlin as accepting as genuine only five cases up to 1940 and they further state that Lietner's case, described in 1949, is the only subsequent example. It would seem, then, that the present case is but the seventh as yet to be recognized.

We are deeply indebted to Drs. S. Moore and D. S. Kahn for their interpretation of the postmortem material.

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SHORT COMMUNICATIONS

CLINICAL EXPERIENCE WITH A NEWER NON-MERCURIAL ORAL DIURETIC–ROLICTON*

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FOLLOWING THE introduction of aminometramide (Mictine) as an effective oral non-mercurial diuretic, there has been a continued interest in the group of pyrimidinedione (aminouracil) compounds in the hope of obtaining a suitable diuretic agent of lower toxicity. Rolicton is one of the aminouracil compounds synthesized by Papesch and Schroeder,[1] under the code number of SC-3656, and the latest of the group to receive extensive clinical trials in the treatment of œdema. Its structural formula is similar to that of aminometramide, differing only in the substituted groups on the uracil nucleus (Fig. 1). Clinical and animal studies have shown this compound to be at least as effective as aminometramide in diuretic activity, and to be far less toxic.[2–5] The mode of action of Rolicton is believed to be similar to that of aminotetramide, one of inhibition of reabsorption of sodium ions by the renal tubule. It does not interfere with the carbonic anhydrase mechanism. The purpose of this study was to measure the initial diuretic response in hospitalized patients with œdema, and to study the effects of long-term treatment in ambulatory patients with congestive heart failure.

*From the Departments of Cardiology and Medicine, Jewish General Hospital, Montreal. This work was supported in part by a grant from G. D. Searle & Co. of Canada Ltd., St. Geneviève, Quebec.

METHODS AND MATERIALS

The clinical material is charted in Table I. Six patients were studied in the hospital, and after discharge, in the cardiac out-patient clinic. Of these, three were men and three were women, ranging in age from 55 to 67 years, and the heart failure was due to hypertension in two, to arteriosclerosis in three, and to rheumatic heart disease in one. Observations were made on 20 ambulatory patients with congestive heart failure who attended the cardiac clinic. Of these, seven were women and 13 were men, ranging in age from 47 to 75 years. The heart failure was due to hypertension in two, arteriosclerotic heart disease in eleven, rheumatic heart disease in six, and cor pulmonale secondary to chronic bronchial asthma and emphysema in one. Among the six patients who were studied in the hospital, three had adequate cardiac compensation at the beginning of the tests with Rolicton. The œdema was kept under control with digitoxin, salt restriction, Neo-merettes (chlormerodrin) tablets daily, and occasional parenteral diuretics. Of the remaining group, two were admitted because of increasing œdema, and the third patient was under a special study,[6] during which his medication was stopped and dietary salt increased. This resulted in a positive salt balance with increase in weight, appearance of œdema and ascites, and increase in dyspnœa and orthopnœa. In this case, plasma volume, using radioactive albumin (Risa), and the circulation times, using dehydrocholic acid (Dycholium) and venous pressure, were also determined. After a suitable control period of at least three days without medication other than digitoxin and a diet containing 3 to 4 g. of NaCl, the Rolicton was administered orally. Patients were allowed to drink *ad lib.* One tablet (400 mg.) was given three times daily for at least three days, and in some instances two tablets (800 mg.) three times daily for another three to four days.

The 24-hour urine excretions were collected and assayed for K, Cl and Na daily both during the control period and while treatment was being given with Rolicton. Serum electrolyte studies were also made before, during and after treatment; these included sodium, potassium, chlorides and CO_2 combining power. The diuretic response obtained with Rolicton in three of these patients was then compared with that obtained with one or more injections of meralluride (Mercuhydrin), 2 c.c. intramuscularly.

The group of ambulatory patients had been under treatment for chronic congestive heart failure for periods ranging from four months to four years (see Table I). At the beginning of the study, most of them were under fairly good control, being treated with injections of mercurial diuretics, digitalis, dietary salt restriction and daily oral diuretic, such as chlormerodrin (Neo-merettes) or aminotetramide (Mictine).

The 20 ambulatory patients were classified as being in moderate to severe congestive failure, in that, in spite of the daily oral mercurial diuretic or aminometramide, they still required from 1 to 5 injections of a mercurial each month to maintain their œdema-free state.

Visits were made to the clinic at least once a week, and the following data were recorded: weight, degree of œdema and symptoms of congestion, such as cough, dyspnœa, and orthopnœa. Serum electrolyte studies were made in ten patients, before, during and after therapy with Rolicton, including serum sodium, potassium, chlorides and CO_2 combining power.

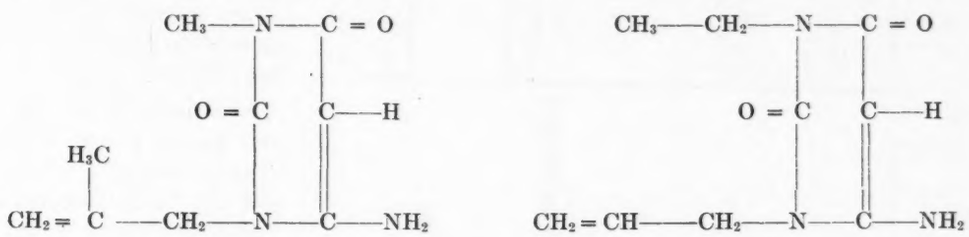

Fig. 1.

In the ambulatory group of patients under observation, the tablets in most instances were substituted for the other oral diuretics, without changing the other forms of their treatment, such as diet or digitalis. At the onset, one 400-mg. tablet was given three times daily, and the dose later increased to two tablets three times daily. In some instances, ammonium chloride was added to the regimen in doses of 60 grains (4 g.) daily for three to four days each week. Injections of a mercurial diuretic were added when the signs and symptoms of congestive failure could not be controlled by Rolicton alone. The duration of therapy with Rolicton ranged from one to 11 months. In this way, not only could the diuretic response be assessed in chronic cases of failure, but also its efficacy could be compared with that of other known oral diuretic agents in the same cases, under similar conditions of diet and environment.

RESULTS

In the six hospitalized patients treated with Rolicton, the diuretic response was more marked in those with definite signs of leg œdema than in the others already œdema-free at the onset of the study. However, in all instances there was a slight to moderate diuresis, as evidence by an increase in the 24-hour urine volume. The water diuresis was accompanied by increased excretion of sodium and chloride in the 24-hour urine, but little change in the urinary excretion of potassium. The chloride excretion closely paralleled the sodium excretion.

Of the three patients with peripheral œdema at the onset of therapy, only one lost his œdema through the administration of Rolicton alone. After 12 days of continuous treatment this patient lost

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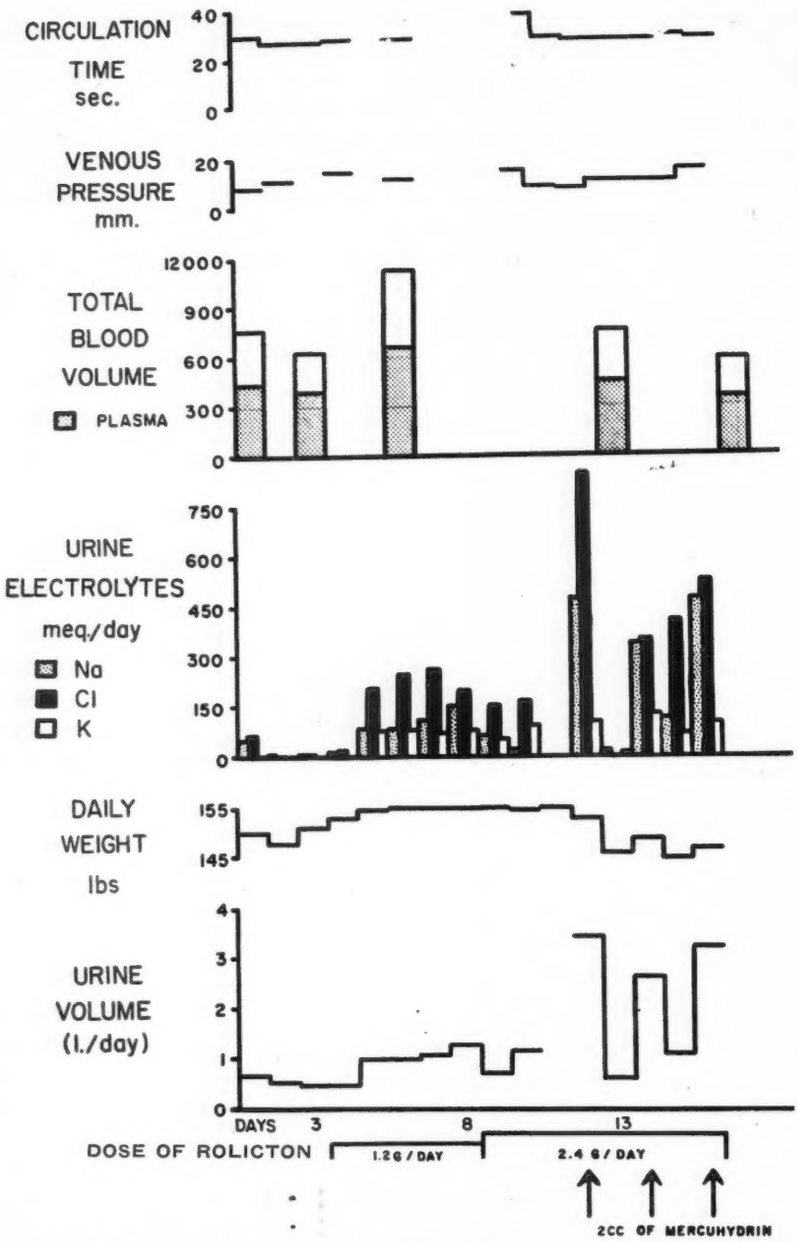

Fig. 2.—Note that although 24-hour urine volumes with the excretion of sodium, chloride and potassium were increased while the patients were on Rolicton therapy, there was no associated weight loss. Compare the marked diuretic response to single injections of Mercuhydrin intramuscularly, which was accompanied by reduction in weight, total and plasma blood volumes, circulation time and venous pressure.

11 lb. of œdema fluid and could then be maintained in this state by the prolonged daily use of 1200 mg. of Rolicton. Although the administration of Rolicton produced an increase in 24-hour urine volume from 800 to 1400 c.c. in another case, the patient still continued to gain in weight (Fig. 2). The addition of 2 c.c. meralluride intramuscularly raised the 24-hour urine volume to 3500 c.c. with a marked increase in the urinary excretion of sodium, chloride and potassium and a considerable drop in body weight. After three such injections every two days, the patient was able to remain free of œdema through the use of Rolicton alone. In the third case of severe heart failure, the use of Rolicton did not alter the œdema, which had to be brought under control by frequent injection of mercurial. When the patients were free of œdema, the administration of Rolicton reduced the need for frequent mercurial injections as required at the onset of treatment. The three patients without signs of peripheral œdema who were previously controlled by the use of other oral diuretics could be maintained œdema-free by the use of Rolicton alone. The administration of mercaptomerin (Thiomerin) to these patients caused only a very small further increase in the 24-hour urine volume with about the same quantities of sodium and chloride in the excreted urine.

The data for the group of ambulatory patients are shown in Table I. In only one case (Case 2) of the 20 was the drug discontinued after two weeks of treatment because of severe nausea, vomiting and anorexia. Of the remaining 19 patients who were treated from one to 11 months, four patients (Cases 6, 8, 11, 12) could be controlled by the use of Rolicton alone. In six others (Cases 4, 5, 7, 9, 13, 15) the frequency of parenteral meralluride injections was reduced; in five patients there was no change in the number of injections required before and after the use of Rolicton (Cases 3, 10, 14, 16, 19). In four patients the number of mercurial injections required to prevent the development of œdema was increased when the patients were treated with Rolicton (Cases 1, 17, 18, 20).

ELECTROLYTE STUDIES

Serum electrolytes were studied before, during and after the administration of Rolicton, and in no instance was there any significant change in the level of serum sodium, chloride, potassium or CO_2 combining power values. Serum non-protein nitrogen values were also studied before and after therapy, and showed no change other than could be expected from the disease state itself.

DISCUSSION

The above results confirm the earlier observations of others that Rolicton has definite diuretic properties, and in the doses used in this series appeared to be a relatively non-toxic and well-tolerated drug.[1–5]

From the results obtained it is evident that although Rolicton may be useful in some instances to initiate a diuresis sufficient to remove œdema,

TABLE I.—NUMBER OF INJECTIONS OF MERCURIAL DIURETICS PER MONTH

Case No.	Age	Sex	Diagnosis	Duration of heart failure in years	Months		Toxic effects			Duration of treatment in months
					Before Rolicton	After Rolicton	Nausea	Vomiting	Anorexia	
1	56	F	R.H.D.	4	2-3	4-5	+	0	0	5
2	66	F	H.C.V.D.	3	1-3	3-4	+	+	+	½
*3	48	F	R.H.D.	2	3	3	+	0	0	2
4	62	M	A.S.H.D.	3	3-6	0-2	0	0	+	11
5	60	M	Cor pulmonale	3	4	0-1	0	0	0	10
6	70	F	A.S.H.D.	⅓	1-2	0	0	0	0	6
7	75	M	A.S.H.D.	2	1-2	0-1	0	0	0	6
8	64	F	A.S.H.D.	⅓	0-1	0	0	0	0	4
9	54	F	R.H.D.	4	3-4	1-3	0	0	0	5
10	52	M	H.C.V.D.	2	1	1	0	0	0	1
11	62	M	A.S.H.D.	2	0-1	0	0	0	0	5
12	61	F	H.C.V.D.	2	0-1	0	0	0	0	4
13	53	M	A.S.H.D.	2	2-3	1-3	0	0	0	4
14	52	M	R.H.D.	3	2-4	2-4	0	0	0	9
15	59	M	A.S.H.D.	1	2-3	0-1	0	0	0	5
16	60	M	A.S.H.D.	3	0-1	0-1	0	0	0	1
17	60	F	R.H.D.	2	1-2	1-3	0	0	0	4
18	47	M	R.H.D.	3	0-1	2	0	0	0	1
*19	68	M	A.S.H.D.	2	0-1	0-1	0	0	0	6
20	64	M	A.S.H.D.	3	1-3	2-3	0	0	0	3

A.S.H.D. = arteriosclerotic heart disease.
R.H.D. = rheumatic heart disease.
H.C.V.D. = hypertensive cardiovascular disease.
*On aminotetramide oral diuretics prior to therapy with Rolicton. All the rest of cases were previously on chlormerodrin.

in most instances with the dosage employed in the series added mercurial injections were required to induce significant diuresis (Fig. 2). Once the patients were œdema-free, Rolicton alone could maintain this œdema-free state in some patients and in many others reduced the requirements for the mercurial injections.

The data obtained from the group of ambulatory patients indicated that the maintenance of the œdema-free state was possible in only 20% of the series with Rolicton alone; in some of the remaining cases it reduced the requirements of mercurial injections. In 75% of the cases studied the response to Rolicton was as good as or better than that obtained with aminotetramide or chlormerodrin. In the remaining 25% of the cases the response to Rolicton was not as good as to the oral mercurial diuretic.

The continued daily use of the diuretic over a long period of time did not lead to a state of tolerance. The prolonged daily administration of Rolicton did not produce any significant alteration in the serum sodium, chloride or potassium in the patients studied. In only one instance was the drug discontinued because of gastro-intestinal disturbances, and no other side effects were observed. Our studies did not contribute to the knowledge of the fundamental mechanism of action of Rolicton.

SUMMARY

The diuretic effects of Rolicton were studied in hospitalized patients and in ambulatory patients with congestive heart failure for periods of up to 11 months.

Rolicton is a safe and well-tolerated oral diuretic and has been found to be useful in the maintenance of patients with chronic congestive heart failure.

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CIRCULATORY ARREST IN COMPLETE HEART BLOCK DURING ANÆSTHESIA AND SURGERY

In patients with heart block, particularly those with prior Adams-Stokes attacks, there is good reason to anticipate circulatory arrest during anæsthesia and operation. Circulatory and respiratory arrest took place in six of 22 individuals with heart block undergoing operation. There were no fatalities. Emergency thoracotomy was performed in one patient but this was probably unnecessary. The patients with heart block were in the older age groups, and mostly in the poor-risk category, because of the underlying heart disease. Those who developed circulatory arrest, with one exception, had had prior Adams-Stokes attacks, and all but one had a major operation. Circulatory arrest probably was precipitated by a number of factors, but the hazards include general anæsthesia, local anæsthesia, and reflex initiation of arrest. It was not shown that the usual pharmacologic means for treatment of Adams-Stokes attacks were uniformly successful either before or during operation. It is not certain that any anæsthetic technique is safe. A plan is offered in the hope of minimizing circulatory arrest and of treating arrest should it occur.—L. D. Vandam and G. A. McLemore, Jr.: *Ann. Int. Med.*, 47: 518, 1957.

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THE HOSPITAL, THE ELDERLY AND THE MENTALLY ILL

Driven to desperation by the incessant demands for more and more oratory, presidents of medical organizations not uncommonly fall back on a philosophical title for their talks, beginning with the word "Whither". Sometimes it is very general—"Whither Medicine?"; sometimes more limited—"Whither the Barium Enema?". Sometimes the title is justified; sometimes it is merely an excuse to string together some unrelated thoughts. One title that ought to figure somewhere in the list is "Whither the Hospital?". Many would consider this topic both timely and controversial, for the future role of the hospital in medical practice must be in many minds.

Beginning as a convenient place for the care of the homeless and friendless sick, the hospital has been forced by the growing complexity of medical care into a position where it dominates the whole of medicine. To such an extent does it dominate medicine that practitioners excluded from hospital privileges regard their exclusion as a tragedy of the first order, while in the United Kingdom the distinction between the sheep practising "hospital medicine" and the goats outside is almost as marked as that portrayed in Scripture.

The main problem for the future seems to be whether the hospital will expand or contract in relation to the sum total of medical practice. Some see in the hospital the natural focus for medical activity, and urge that it should throw its benevolent light on corners of the medical scene hitherto reserved for individual practitioners. Others, mindful of the immense amount of money required to run hospitals and the difficulty of recruiting adequate personnel as well as the general overcrowding, urge that methods be sought for curtailing the hospital's activities and keeping the maximum possible number of patients under domiciliary care. The latter tendency is of course increasingly thwarted by social factors outside the control of the medical profession, such as the contraction in numbers of the average family, the general decline in filial piety, and the greatly lowered incidence of unmarried and unemployed female members of a family.

In our January 1 issue, Dr. Horbaczewski touched on one facet of this problem, when he lamented the unnecessary admission of elderly persons to mental hospitals. He might equally well have added to this theme the unnecessary admission of the mentally ill to mental hospitals. Since these two areas of medicine require scrutiny, it might be as well to mention some recently publicized attempts to deal with the problems. The Nuffield Provincial Hospitals Trust has recently reported on an experiment undertaken by the Geriatric Unit of the Belfast City Hospital, Northern Ireland.[1] This was an attempt to bring rehabilitation of the elderly into the home, and was based on the premise that patients to be treated were already getting good home care but lacked physiotherapy. The general practitioner was responsible for first referral of the case; only one-third of those referred were found suitable for treatment (mainly hemiplegics and arthritics). Out of those selected, two-thirds made satisfactory progress with physiotherapy.

Another writer has recently described[2] the operation of a geriatric hospital unit for temporary stay of older persons whose continued presence in a home was causing domestic stress. A system whereby the patient (hemiplegic, osteoarthritic, parkinsonian, or with an old femoral fracture) spends six weeks in hospital, followed by six weeks at home, followed by readmission for six weeks and so on, was found highly satisfactory in a series of 100 patients. During their admission, patients were given not only physical rehabilitation, but also therapy catering for their emotional and social needs; at the same time, their sons and daughters gathered strength for a further bout of home care.

Two alternative systems for the care of the mentally ill outside hospital have recently been discussed in the *Lancet*.[3, 4] Wing comments on family care systems in Norway and Holland, whereby patients live in private homes, not their own, under general psychiatric supervision. In Norway, 39% of certified mentally ill patients are in private family care under supervision from a mental hospital or by the state. Those placed in families include mental defectives, chronic schizophrenics and a few epileptics unable to fend for themselves; this type of care will be developed for convalescent psychotics and neurotics. Holland has already a long tradition of family care, whose results are surprisingly good. In both countries the system appears to work well. The patients are accepted by the community and cause little trouble.

The town of Worthing in England has recently been the centre of an experiment[5] in which patients who in the past would have been committed to a mental hospital have been kept at home with their families and treated either at out-patient interviews at the mental hospital or by domiciliary visits paid by psychiatrists. The experiment is

essentially a two-year research project, but the first ten months of its operation have shown how greatly such an out-patient service can ease the strain on the mental hospital. During its operation it has lowered the admission rate to the mental hospital by 59%. At the First Canadian Mental Hospital Institute (Toronto, January 22, 1958), Dr. W. S. Maclay of London, England, referred to the Worthing experiment and made it clear that the trend in the U.K. is towards providing substitutes for mental hospital beds rather than the other alternative—increasing the number of beds. In Canada, a similar choice awaits us, not only as regards mental hospital beds, but also as regards hospital beds in general.

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Editorial Comments

THE PRECANCEROUS LESION

The importance of the precancerous lesion is proved clinically. Various precancerous lesions have been shown by experience to be followed by a higher than coincidental development of cancer. In human material, accepted precancerous lesions are leukoplakia of the mucosal surfaces, various keratotic lesions of the skin, and polyps of the intestine; some authorities suggest such lesions as cystic mastitis, cirrhosis of the liver, and squamous metaplasia of respiratory epithelium.

An approximate equivalent of the precancerous lesion has been sought in experimental studies of changes preceding development of tumours in animals by application of chemical carcinogens. The results of these studies appear to indicate: (1) that in some cases, morphological changes similar to those of the human precancerous lesion can be observed to precede the appearance of malignant tumours; (2) that in other cases, morphological changes may persist indefinitely without giving rise to malignancy; and (3) that frequently no morphological change is found to precede the appearance of malignancy. Therefore, even if it is accepted that the pathogenesis of the common cancers in man is similar to that of chemically induced cancers in animals—and we do not have sufficient evidence to support such a parallelism—the precancerous lesion cannot be regarded as *necessarily* possessing or harbouring incipient malignant properties.

The experimental evidence suggests that some cancers arise because of the combined action of several systemic and local factors. A morphologically recognizable precancerous lesion, as observed clinically, could represent the earliest visible expression of some of the factors producing it. However, unless all the other necessary requirements were fulfilled it never would become a true cancer and therefore is only a degree more prone towards the development of malignancy than normal structures. Theoretically, it is possible that eventually all precancerous lesions might become malignant, provided there was sufficient time for these and other factors to act; in the author's opinion, additional factors are *necessary* for malignant transformation to occur.

From a clinical point of view the removal or treatment of precancerous lesions, which are known to lead to malignancy in a higher proportion of cases, is certainly justified, as by doing this we decrease the chance of development of cancer in that area. From an academic point of view, studies of known precancerous lesions with regard to all known factors affecting cell division, such as enzyme systems, viruses, hormones, mutagenic agents and tissue organizers, may yield important information as to the nature of malignant transformation. On the other hand, we have to realize the fact that not all etiological factors produce morphological changes prior to cancer formation and that an extensive search for such changes in many types of malignancy might be in vain.

STANLEY C. SKORYNA

REGIONAL ENTERITIS

Despite the fact that the original clinical description of regional enteritis is 25 years old, recent months have witnessed a striking resurgence of interest in its prognosis and treatment. This is of course the result of the added publicity accruing to the disease by virtue of its attack on the President of the United States.

Very little that is medically newsworthy has resulted from the recent recrudescence of interest in this chronic and frequently dangerous affliction. Most groups of investigators[1, 2] are in agreement as to the techniques for accurate diagnosis; it seems clear that retrograde barium studies, if unsupplemented, will miss the diagnosis in a respectable proportion of cases. For actual roentgen visualization of typical or atypical lesions in a reasonable percentage of patients, careful x-ray examination of the small bowel is mandatory.

Although there is fairly close agreement in the matter of accurate diagnosis, there is little unanimity of opinion as to prognosis or treatment. One carefully prepared and well-documented study[1] suggests that the final results of palliative treatment—especially roentgenotherapy—are at least as satisfactory as those following surgery. Another equally capable group of investigators[2] considers that surgery will be required in 80% of cases, and that even of surgically treated patients 20% will have a recurrence.

This discrepancy may be the result of inadvertent case selection, one treatment centre having accidentally been associated with a preponderance of mild cases and the other with an overwhelming proportion of severe ones. It may of course also be due to abbreviated and inadequate trials of medical (especially roentgen) therapy in a surgically orientated group.

As is usually the case in such disagreements, the answer probably lies midway between the two extremes. As a rule, patients should undoubtedly receive the benefit of all available forms of medical treatment, including roentgenotherapy. If these are unsuccessful, or if the disease has been unusually severe, and especially if it was obstructive in character, surgery should be the treatment of choice.

There appears to be no significant disagreement that the eventual prognosis is good, if effective treatment drawing on all available modalities is carried out.

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UREA AS A DIURETIC

Most physicians have had cases of congestive heart failure in which the failure became intractable and the condition apparently irreversible. It is highly unlikely that, at this juncture, any of us would have fallen back on that ancient, somewhat discredited, but surprisingly physiological diuretic, urea. Yet this is exactly what two cardiologists at the London Chest Hospital have done, and their results are reported in a recent number of the *British Medical Journal*.[1]

Their series comprises 17 patients with obstinate and prolonged right ventricular failure in whom anasarca and ascites were the main features, and in whom all known measures for the control of congestive cardiac failure, including digitalis, mercurial diuretics, rigid sodium restriction and intracardiac surgery had proved ineffective. Wherever possible (14 of 17 patients) the treatment was carried out in hospital, and consisted in the addition of urea up to 45 g. daily (never less than 30 g.) to the patient's therapeutic regimen, which had previously been demonstrated to be ineffective in controlling œdema. Most patients found no difficulty in taking this dose, especially if dissolved in grapefruit juice, and, with two exceptions, the subjects have been continued on treatment for periods varying between 2½ weeks and 7 years.

It appears that in some cases of this type, urea, in average doses, may be expected to suppress fluid retention, potentiate the effect of mercurial diuretics, prevent gross rebound following mercurials, and even eliminate the need for mercurial injections. Smaller doses may merely enhance the effect of mercurial diuretics and abolish rebound, without entirely restoring positive fluid balance. In some cases, spectacular diuresis may occur with the patient on urea alone after mercurial injections have become ineffective. Diuresis with urea is due to a rise in blood urea after its ingestion. The excess of urea circulating in the blood leads to the filtration of large amounts of urea from the glomeruli. The rising concentration of urea increases the osmotic pressure in the renal tubules, hindering reabsorption of water. Urea thus retains water in the tubules for its own elimination.

The writers are the first to concede that, as cardiac strength wanes, osmotic diuresis fails, because glomerular filtration becomes deficient. However, in any specific patient, it is impossible to foretell when this will occur; and even in apparently hopeless cases, a good diuretic response may disclose an amazing amount of cardiac reserve. It is questionable whether treatment with urea prolongs life. What life remains, however, may be rendered more bearable by the clearance of œdema, the relief of general discomfort, and the consequent increase in the sense of well-being. Such advantages are not to be dismissed lightly; and it would appear that urea deserves a therapeutic trial in selected cases of "intractable" heart failure.

S.J.S.

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Medical News in brief

COMPRESSION OF BONE ENDS AS AID TO FRACTURE UNION

Opinions differ on the value of application of compression to the bone ends as an aid to union in fractures. King of Melbourne, Australia (*J. Bone & Joint Surg.*, 39A: 1238, 1957) studied the effect of compression of the bone ends in 49 cases of ununited fractures. He countersank one bone end and pointed the other to get greater contact of cancellous bone, bored drill holes near the fracture site to promote revascularization, and applied compression by inserting two wires or pins above and below the fracture site respectively and approximating the latter either by stretching in a stirrup or application of heavy rubber bands to the ends of the pin. He achieved union in 41 out of the 49 ununited fractures; 12 of the 13 with infection and sinus formation united, and the sinuses healed; four recent fractures with gross displacement also united. He thinks that compression does not shorten the period required for bone union, but that its real value is in the treatment of infected and ununited fractures, especially in the lower third of the humerus and upper half of the tibia. Apparently the greater amount of cancellous bone present there favourably affects results. He does not advise use of compression in recent fractures, especially if the fracture is near a joint.

ASYMPTOMATIC ENLARGEMENT OF THE PAROTID GLANDS

Inspection for enlarged parotid glands yielded 40 cases among 2000 admissions to a hospital in New York State over a two-year period (J. J. Duggan and E. N. Rothbell, *New England J. Med.*, 257: 1262, 1957). These 40 patients and 10 additional ones contributed by other physicians were carefully questioned regarding past or present inadequacy of diet. Liver function tests and liver biopsies as well as standard laboratory investigations and glucose tolerance tests were carried out whenever feasible. In this series, 44 patients gave a history of abnormal diet, 41 were alcoholics and 25 were considered to have cirrhosis of the liver. Another 10 were thought to have fatty liver and one had pericholangitis. The parotid glands were enlarged bilaterally, were neither warm nor tender, and felt smooth and firm. Enlargement of other salivary glands was not striking. Sthenic habitus predominated among the patients, and except for three all the patients were calorically well nourished. A tendency to diastolic hypertension was evident and hyperglycæmia was found in 32 patients.

Reviewing reports of bilateral enlargement of the parotid glands from various countries, the authors note the similarity of certain features in European and American patients; obesity, diabetes mellitus, alcoholism and liver disease are frequently associated. In Asian peoples parotid enlargement is endemic and appears to be most commonly associated with nutritional deficiencies. Protein-free diets have produced parotid-gland enlargement in rats. In kwashiorkor, mumps-like swelling was observed on feeding patients large amounts of proteins. Malnourished prisoners of war and camp inmates showed bilateral swelling of the parotids on rapid refeeding.

The authors conclude that bilateral parotid enlargement seems to accompany disturbed nutrition, possibly protein deficiency.

HÆMORRHAGE FROM THE UPPER GASTRO-INTESTINAL TRACT

Out of 300 cases of gross hæmorrhage from the upper gastro-intestinal tract encountered in a Pittsburg hospital in five years (*J. A. M. A.*, 165: 1899, 1957), peptic ulcer of stomach, duodenum or jejunum was responsible for the hæmorrhage in 70% of cases, and duodenal ulcer was the characteristic lesion in patients under 40. Above 41 years of age other causes became common, including œsophageal varices associated with cirrhosis of the liver. In older patients, complicating diseases such as cardiovascular disease, chronic pulmonary disease, chronic nephritis, obesity, alcoholism or acute infection were serious factors. The universal symptom of such hæmorrhage was melæna. Hæmatemesis occurred in 60% and initial syncope in 10%, while signs of profound shock were observed in 15%. While the history and physical examination gave useful leads in diagnosis, the latter was based mainly on evidence obtained by radiography, endoscopy or surgery. The cause of bleeding was undetermined in only 8% of the series. Where bleeding failed to cease promptly on admission to hospital, or where it recurred, the patient was taken to be in danger of irreversible shock; when the site of bleeding was thought to be in the stomach, duodenum or jejunum, emergency surgery was then undertaken. The crude mortality rate of 14% for the series shows the gravity of the condition; this gravity often stems from coexistence of other disease.

INTELLIGENCE AND INFLUENZA

It is frequently asserted that mental defectives are also physically defective, and that the incidence of physical defect and disease, no matter what its particular form, tends regularly to increase as the intelligence quotient decreases. The recent epidemic of Asian influenza in South Africa afforded an opportunity to test this statement with regard to influenza in an institution for the mentally defective. Results, which are reported in the *South African Medical Journal* (31: 1237, 1957), showed that among a population of idiots, imbeciles and morons, no one group was more susceptible to illness in general. At first it appeared that there was a correlation between the intelligence quotient and the incidence of Asian influenza, but this proved to be incorrect, since correlation was really between chronological age and incidence. When the age factor was allowed for, the correlation disappeared. A further survey covering all illnesses also led to a similar conclusion, namely that intelligence per se appears to be rarely a factor in the incidence of disease among mental defectives.

(Continued on advertising page 54)

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Special Article

TRANSFUSION OF GIRLS AND WOMEN CAN KILL THEIR BABIES*

A NOTE ADDRESSED MORE TO SURGEONS AND ANÆSTHETISTS, BUT APPLICABLE TO OTHERS

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I ADDRESS THIS NOTE more to surgeons and anæsthetists than to others, although the facts are applicable to the practice of most doctors. A surgeon often knows a patient only for days, and an anæsthetist for hours or minutes; the bad effect of a transfusion that either one may give may not become apparent for years; it may never be known to the man who gave the transfusion. I illustrate by four cases, two surgical, one medical, one obstetrical or gynæcological.

In 1948 Mrs. B. had an operation for a herniated intervertebral disc, during the course of which she was given a transfusion. Neither she nor her family physician knew of this transfusion until the events of pregnancy indicated that it must almost certainly have taken place; it was then proven by the hospital record. Mrs. B.'s blood was first examined in May 1950 in the second month of her first pregnancy; it contained an anti-Rh antibody with a titre of 2. At four months the titre had risen to 256. At six months it was 1024 and the fetus died. Autopsy proved that the fetus had had erythroblastosis. In 1951 her next fetus also died.

On April 20, 1940, Adele S., aged 6, was playing round a bonfire; her clothes caught fire; she was admitted to the Children's Hospital, Winnipeg, with third-degree burns involving about two-thirds of the skin. There she remained for 12½ months, during which time she received three transfusions, to the third of which, given some seven months after the first, she responded with a chill, sweating and fever. *Fifteen and a half years later,* on November 23, 1955, when she was in the second month of her first pregnancy an anti-Rh antibody with a titre of 1 was found in her blood. It continued at this level until three weeks before her expected date of delivery, when it rose to 256. Her attending obstetrician, Dr. J. R. Mitchell, induced labour at once. The amniotic fluid was yellow, containing 0.83 mg. of bilirubin per 100 ml. The baby, a boy weighing 5 lb. 4½ oz., appeared very ill at birth. The cord blood hæmoglobin was 10.82 g., and the bilirubin 9.6 mg. per 100 ml. The baby was given four replacement transfusions in 48 hours by Dr. W. D. Bowman, and made a complete recovery; it was a close call.

When Mary N., then in her teens, had typhoid fever in 1936, she was given a transfusion of her mother's blood. She married six years later and the following year had a nice normal baby. The next year, however, she gave birth to twins, one hydropic and the other macerated. She was Rh-negative, her mother Rh-positive, her first child Rh-negative. It was *eight years* from the time of her transfusion to the death of her first Rh-positive babies. *Seventeen years* after that poisonous transfusion she lost her second Rh-positive baby, stillborn. Luckily her husband is heterozygous and can father some Rh-negative babies.

This is not written in criticism of the fact of transfusion in these cases, although the need in the first case is open to doubt. It is written to illustrate the fact that transfusion of girls or women may years later kill their babies; the time intervals between transfusion and disaster in these three cases was 2 years, 15 years and 8 years; we have been able to demonstrate Rh antibodies as long as 30 years after the last possible antigenic stimulus.

The inciting factor in each of the above cases was Rh-positive donor blood given to an Rh-negative patient. It may be objected that sensitization by this means no longer occurs. But this is not so. Mistaken typing of blood as Rh-positive or Rh-negative still occurs; a fatal transfusion reaction due to just such faulty typing was recently reported in this *Journal.*[1] Beyond simple Rh-positive and Rh-negative incompatibility there are other incompatibilities. The Rh blood group system itself is complex. For example, about 20% of Rh-positive people are of such an Rh-positive subtype (CDe.-CDe or R_1R_1) that about 80% of Rh-positive donors and practically 100% of Rh-negative ones are incompatible with them; the antibody that they are likely to develop is an anti-Rh antibody called anti-c. The following case is an illustration.

Mrs. McP., Rh-positive, suffered an accidental abortion in 1952, and, as part of her treatment, was given a transfusion of Rh-positive blood. In 1955 she gave birth to a baby who quickly became deeply jaundiced and required two replacement transfusions. Mrs. McP. was found to be of the above Rh-positive type, i.e. CDe.CDe; her blood contained anti-c of the Rh system and also anti-K of the unrelated Kell blood group system, both being the result of the 1952 transfusion. The baby's erythroblastotic jaundice was due to the anti-c. Her next baby died in spite of transfusion.

I could cite you many other examples of transfusion sensitization from our files, but do I make my point? Transfusions of girls and women can kill their babies, often many years later.

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*From the Rh Laboratory, 735 Notre Dame Ave., Winnipeg 3, and the Department of Pædiatrics, University of Manitoba. This is the second of three articles.

CHLORPROMAZINE TOXICITY

In a German laboratory, prolonged administration of large doses of chlorpromazine to cats, rabbits and dogs failed to produce any liver damage. If the liver had been previously damaged with carbon tetrachloride, chlorpromazine failed to aggravate the liver damage. This finding supports the opinion of German clinicians that chlorpromazine is not a specific liver toxin, in contrast to statements from American and Canadian sources.—W. Wirth: *Deutsche Med. Wchnschr.*, 82: 1745, 1957.

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REVIEW ARTICLE

THE CURRENT STATUS OF THE TRANQUILLIZING DRUGS*

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ONE OF THE MOST pressing problems in medicine today is the evaluation of the new drugs known as tranquillizers. The tenor of publications on the subject has been mostly one of acclaim. Recently, however, the misuses and side reactions of these agents have received strong emphasis.

Therefore, a review of some 150 current articles and some unpublished data on clinical experiences with tranquillizers was undertaken to determine, on the basis of recorded observations, what percentage of patients in different diagnostic categories have improved and what principal side-effects and risks are entailed by their use.

Reports that enumerated and included controls and those giving diagnostic or therapeutic criteria were given preference. Grouping the variously termed diagnoses, never entirely successful, is a necessary part of assembling medical statistics. Each author's terminology was maintained when possible and his judgment of patients' improvement was taken at face value; only moderate or better degrees of improvement were counted. Much of the data is presented in cumulated form from several sources which, however, are named. When results were not in reasonable agreement, they were not cumulated.

THE CLASSIFICATION OF TRANQUILLIZERS

When asked how they felt after receiving these drugs, 95% of one group of patients used the word "calm" in their replies, but no term, including "tranquillizer," adequately describes the actions of these drugs. They can hardly be classified for clinical purposes beyond grouping together the phenothiazine derivatives and Rauwolfia alkaloids, which may bring improvement or remission of a psychotic state, and the milder-acting agents, with weak or no antipsychotic effects. The milder-acting agents are sometimes used as adjuncts in the treatment of severe mental illness but are generally prescribed for neuroses, particularly those accompanied by anxiety or tension states, and for reactions to environmental stress. Any of the tranquillizers may be indicated for various special purposes in nonpsychotic individuals.

DRUGS WITH POTENT ANTIPSYCHOTIC EFFECTS

Chlorpromazine

The cumulated data of 3543 psychiatric patients who were treated with chlorpromazine (Largactil, Thorazine) are presented in Table I in order to compare the percentages improved among various diagnostic or descriptive categories.

TABLE I.—THE PERCENTAGES OF 3543 PATIENTS SHOWING IMPROVEMENT (CUMULATED DATA) ON CHLORPROMAZINE, IN DESCENDING ORDER OF EFFECTIVENESS

Diagnostic or descriptive category	*Number patients treated*	*Per cent of patients improved*	*Authors (see references)*
Manic psychosis.....	35	95	1, 2, 3
Senile, agitated.....	272	85	4, 5, 6, 7, 8
Schizophrenia.....	362	83	1, 4, 9, 10, 11
Endogenous depression	23	83	2
Hospitalized psychiatric cases....	1523	82	12
Anxiety reactions.....	81	80	1, 5
Chronic psychotics....	368	78	9, 10, 13, 14, 15
Conversion reactions..	45	62	5
Reactive depression...	29	55	2, 5, 9
Psychoneurosis (type unspecified)...	652	43	4
Manic depressive.....	69	36	16, 17
Psychosomatic illness.	59	34	18
Chronic anxiety or chronic neurotic tension.....	26	0	14, 19

Ninety-five per cent of patients diagnosed as manic psychosis in contrast with only 36% of those listed as manic depressive psychosis improved. As a rule, pure depressives do not respond favourably to chlorpromazine, although in one group of 23 cases of endogenous depression, 83% improved.[2] Most authors agree that electroconvulsive therapy, insulin coma, and prefrontal lobotomy still have a place in the treatment of severe depression.

The second highest percentage of patients who improved on chlorpromazine was in the senile agitated and senile psychotic group. Of patients listed as hospitalized chronic psychotics, 78% improved, but in schizophrenics, alone, improvement occurred in 83%. Experience has shown that whereas about 80% of acute cases respond, only 50% of chronic schizophrenics (duration of illness over two years) are benefited.[20] An interesting fact not apparent from figures in Table I is that 26% of 485 hospitalized schizophrenic patients graduated to full convalescence or gained release.[16, 17]

Results were unimpressive in the treatment of psychoneuroses (types unspecified) and in chronic anxiety or chronic neurotic tension, although 80% of one group with anxiety reactions (possibly acute) responded favourably. Some patients with reactive depression or conversion reactions and a few with phobias or obsessional neurosis benefited,[4, 5] but, in general, poor results can be expected from chlorpromazine therapy in ambulatory patients with obsessive compulsions, hypochondriasis, hysteria and character disorders.[4, 21]

Chlorpromazine provided effective sedation in acute alcoholism[22] and in head injuries (producing a light sleep from which the patients can be aroused for neurological examination).[23] The drug augments the action of barbiturates and narcotics[24] and has been used successfully to reduce narcotic requirements and awareness of pain in terminal

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malignancy and other conditions causing intractable pain.[9, 25] Nausea and vomiting of pregnancy and vomiting and anorexia caused by radiation therapy may be relieved by the antiemetic action of chlorpromazine.[14, 25, 26]

If chlorpromazine is to be used in chronic conditions, the period of trial should be at least six to eight weeks, and the therapy should be considered as chlorpromazination.[4] It does not alter the basic structure of a psychosis and must be continued indefinitely. Old symptoms are likely to return within two or three months after the drug is discontinued.[1, 16]

Reactions to chlorpromazine may be divided into allergic phenomena and side-effects of a pharmacologic nature. Jaundice, agranulocytosis, and skin rash are allergic reactions that can occur with small or large doses.

Jaundice appears variously in from 0.4 to 1.4% of cases in large series.[4, 27–30] It usually commences two or three weeks after the start of therapy and clears spontaneously. The results of liver function tests are similar to those in an obstructive type of jaundice.

Agranulocytosis is a more serious reaction that appears in about 0.3% of cases, usually within 20 to 60 days after the beginning of therapy.[27, 31] It is preceded by fever and sore throat, which are important warning signs[32] because when such cases are recognized early and the medication is stopped, the patient generally recovers.[33] Patients with agranulocytosis or leukopenia due to chlorpromazine should not be re-treated with any phenothiazine derivative.

Skin eruptions, sometimes accompanied by œdema, are allergic in nature and occur in about 6% of cases.[3, 5, 10, 13, 15-17, 27, 29, 34] The drug also produces increased sensitivity of the skin to sunlight in about 2% of patients.[4, 27]

The following side-reactions are pharmacologic effects of the drug. Symptoms of parkinsonism occur in about one-fifth of patients, according to Goldman[27] and Kinross-Wright,[34] but were reported by Hall *et al.*[35] in 40% of 90 patients (highest incidence in hebephrenics). However, full-blown parkinsonism is not likely to occur until the dosage exceeds 2 grams daily, according to Ayd.[36] Some degree of drowsiness may be noted in up to three-fourths of patients; it interferes with daily activities in about one-fourth[4] and amounts to severe somnolence in about 2% of patients.[27] Chlorpromazine also produces an orthostatic hypotension which is severe in about 1.5% of cases.[27, 31] Other side-effects are breast engorgement and secretion, tachycardia, palpitation, dizziness, miosis, fever, increased appetite and weight gain, lethargy, increased dreaming, confusional state, and feelings of unreality and depersonalization.

The drug should be given with extreme caution to patients with hepatic decompensation, a potentially dangerous hypotensive tendency, or severe degenerative cardiovascular disease. On the other side of the ledger, the patients who require chlorpromazination are usually so seriously ill and the outlook is so discouragingly bleak that otherwise annoying side-effects fade in importance. The few toxic reactions and many side-effects of chlorpromazine therapy must be weighed against the dangers of: (1) electroconvulsive therapy, insulin coma, or lobotomy; (2) ineffective psychotherapy because of lack of rapport; (3) allowing an acute or subacute psychosis to become confirmed, or a chronic psychotic to remain symptomatically ill for indefinite periods of time, often until death; (4) physical violence to the untreated or incarcerated patient inflicted by self or others.

Promazine

Promazine (Sparine) is more effective in acute than in chronic psychotic patients.[37] Hallucinations may not be abolished but they cause less concern.[38] Azima[39] observed improvement in about half of 26 chronic schizophrenics and noted that agitated paranoids were helped more than other types.

Likewise, the manic type of manic depressives responded well, whereas the nonagitated depressives did not.[39, 40] Promazine was of value in 19 cases of chronic brain syndrome[40] and 274 cases of alcoholism.[38, 40, 41] The withdrawal illness was minimized in several opiate and barbiturate addictions.[38, 40, 41] Several patients with anxiety have improved;[39, 40] poor results were obtained in character neuroses,[39] phobias,[41] and hysteria.[39]

Toxicity studies in 100 cases demonstrated an elevation of alkaline phosphatase in four cases but no jaundice, hæmatological, or extrapyramidal complications.[39]

Drowsiness bothered outpatients; however, they did not complain of lethargy.[39] A few instances of mild to moderate hypotension, with syncope in one, were reported.[38, 42] Dizziness and reduced salivation occurred[40] and four of 100 patients developed œdema of the face or extremities.[39] Parkinsonian tremor has been noted and three of 191 patients had grand mal seizures possibly brought on by the drug.[37, 39]

Proclorperazine

Proclorperazine (Compazine) gave excellent results in 21 of 38 mildly disturbed nonhospitalized psychoneurotic patients.[43] It is recommended for short-term (up to two weeks) therapy in anxiety or tension states or in mild to moderate agitation but, at present, is not advised for severe psychotic conditions.

Proclorperazine successfully decreased the awareness of pain in 31 of 50 patients.[44] It has a potentiating effect with opiates and barbiturates, and it also has a potent antiemetic effect, bringing relief of nausea and vomiting in 29 of 40 patients, most of whom were in an advanced stage of carcinoma.[45]

Side-effects are minimal and consist chiefly in drowsiness[43] and dry mouth;[45] the most frequently troublesome reactions (with the larger doses) are motor restlessness, tremor, and parkinsonism.[21]

A carefully controlled study of the pharmacological effects of proclorperazine in 24 subjects showed very little decrease in mental abilities tested but some decrease in performance involving muscular co-ordination.[46]

Mepazine

In a series of 250 patients, Bowes[47] found mepazine (Pacatal) especially useful in the control of manic and schizoaffective psychotics. Improvement has been observed with mepazine therapy in eight of 10 acutely ill psychotics[37] but less than half of 168 chronically ill psychotic patients.[37, 48] Even less antipsychotic effect was demonstrated by Lomas,[49] who compared mepazine and chlorpromazine in two groups of 50 schizophrenics each. Moderate or better improvement occurred in 37 patients on chlorpromazine and 29 patients on mepazine; their data left little doubt that chlorpromazine was the superior drug in these cases.

Feldman[48] investigated the effects of mepazine on individual symptoms in 118 chronically ill patients refractory to other therapy. Improvement was observed in about one-third of instances of hyperactivity, tension, hostility, and combativeness and one-fourth of instances of negativism and hallucinations. Appetite and sleep increased in one-third of patients and there was improved amiability, sociability, appropriateness of conversation and participation in about one-fourth.

One fatality from agranulocytosis during mepazine therapy was recently reported.[50] Other possibly troublesome reactions are granulocytopenia, toxic psychosis, jaundice (two of 130 patients), and dermatitis.[21, 48] Large doses may cause parkinsonism.

Side-effects in the descending order of frequency are dizziness (30%), drowsiness (25%), blurring of vision (12%), gastro-intestinal symptoms (9%), hypotension (8%), slurring of speech (6%), and dry mouth (5%).[48]

Perphenazine

In a double-blind study comparing perphenazine (Trilafon) with chlorpromazine and a placebo in 75 overactive patients with anxiety, Mason-Browne[51] concluded that perphenazine was more effective than chlorpromazine as shown by quantitative tests of behaviour. Side-effects, which occurred in seven of 25 patients, were mild.

Perphenazine was also administered to 25 elderly patients with severe neurotic reactions or various psychoses, and improvement was reported in 19. The drug relieves anxiety, calms agitated and excited patients, and is antiemetic. It is recommended especially for geriatric patients.[52] It is not effective in endogenous depression.[21] None of 50 patients showed evidence of toxicity or hypotensive reactions.[51, 52] It may produce dry mouth, weakness, miosis, aching extremities, dreams, motor restlessness, tremulousness, or parkinsonism.

Reserpine

In 22 articles dealing with reserpine or other Rauwolfia alkaloids, this most historical of all tranquillizers often appears as the drug of choice for the control of agitated, hyperactive, assaultive, or destructive behaviour and for prolonged maintenance of the chronically disturbed patients who respond to it. The Rauwolfia alkaloid group includes powdered whole root of *R. serpentina* (Rauwiloid, Raudixin), reserpine (Sandril, Serpasil), rescinnamine (Moderil), and deserpidine (Harmonyl).

Kline[53] clearly demonstrated the sedative effect of these drugs in a careful study of 411 hospitalized psychotic patients. In later investigations in which larger doses were used, five authors[54–58] observed improvement in 59% of a total of 808 psychotic patients given reserpine. It appears that not as many respond to reserpine as to chlorpromazine, but reserpine is the safer of the two, an important point when long-term therapy is required. The percentages of 1254 patients showing improvement on reserpine are listed in Table II by diagnostic or descriptive categories.

TABLE II.—THE PERCENTAGES OF 1254 PATIENTS SHOWING IMPROVEMENT (CUMULATED DATA) ON RESERPINE, IN DESCENDING ORDER OF EFFECTIVENESS

Diagnostic or descriptive category	*Number patients treated*	*Per cent of patients improved*	*Authors*
Acutely disturbed aggressive adolescents	25	100	59
Manic psychosis	16	100	2, 56, 60
Irritable hypertonic infants	32	90	61
Anxiety and tension states	53	83	60, 62
Senile, disturbed	89	80	63
Psychosis (type unspecified)	808	59	54, 55, 56, 57, 58
Paranoid schizophrenia	119	54	2, 3, 62, 64, 65
Psychosomatic illnesses	112	46	18, 66

Agitated patients of any age, despite widely diverse diagnoses, are most likely to benefit from reserpine. For example, all of 16 manic psychotics became quiet and tractable;[2, 56, 60] the bizarre behaviour of 90% of 32 irritable, hypertonic infants changed to nearly normal;[61] and nearly 80% of 89 difficult to manage senile patients responded favourably.[63]

Parenteral reserpine is of value in acute situations. In the experience of Nicolaou,[59] all of 25 schizophrenic or acutely disturbed aggressive nonpsychotic adolescents improved immediately after receiving the drug in this form; about half

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of them thereafter maintained good results on oral therapy. As expected, although only 54% of 119 patients with paranoid schizophrenia improved on reserpine,[2, 3, 62, 64, 65] the response of the hyperactive paranoids was better than that of the more quiet catatonics or hebephrenics.[2, 3, 64, 65] On the other hand, reserpine has been found particularly useful in preventing relapses in catatonics after electroconvulsive therapy.[13]

Psychoneurotic anxiety and tension states also appear to respond well.[60, 62] However, the new, milder-acting tranquillizers with fewer side-effects may be preferred for mild or moderate cases, except when hypertension responsive to reserpine is present. Reserpine may be worthy of trial in certain psychosomatic conditions (other than gastro-intestinal)[18, 66] and, possibly, in chronic idiopathic enuresis in children.[67]

Like chlorpromazine, reserpine is symptomatic rather than curative therapy and often must be continued indefinitely. Also, it is slow to take effect; several months' trial may be required. In pure depression, or apathetic melancholia, Rauwolfia therapy carries a risk of producing further mental depression and sometimes suicidal tendencies.[68]

Jaundice and agranulocytosis are not problems with reserpine. Drowsiness of some degree occurs in up to three-fourths of patients[69] and is severe in about 2.5%.[27] Nasal stuffiness and dreams are common complaints.[70]

The incidence of other side-effects in a series of 442 patients was reported as follows: parkinsonism 14.7%, salivation 2.5%, œdema 2%, convulsions 2%, skin eruption 1.6%, and nausea and vomiting 1.4%; depression and anxiety, severe hypotension, fever, bradycardia, and excessive weight gain occurred in less than 1% of patients.[27] Gynæcomastia may be observed.[32] Diarrhœa is occasionally encountered, and gastric acidity is increased with parenteral therapy. Therefore, the drug should be used cautiously in patients with peptic ulcer or ulcerative colitis.

MILDER-ACTING AGENTS WITH LITTLE OR NO ANTIPSYCHOTIC ACTION

Hydroxyzine

Hydroxyzine (Atarax) is one of the milder-acting tranquillizers of value in anxiety states, senile excitation, emotional stress, and various psychosomatic disorders. Hydroxyzine was effective in 70% of 113 patients with anxiety states[71, 72] and 95% of 54 cases classified as senile anxiety.[73] In emotional stress associated with dermatoses the drug gave subjective improvement in 83% of 159 patients and objective improvement in 88% of 41 patients.[74] In various psychosomatic disorders, hydroxyzine was deemed of value in 62%.[71] It was ineffective in moderate to severe depression and hysteria.[72]

No toxicity was noted in a cumulated total of 442 patients receiving hydroxyzine reported by four authors.[71-74] Side-effects were infrequent except for increased intestinal peristalsis,[71] and otherwise consisted of mild rhinorrhœa, weight gain, dry mouth, itching, drowsiness, unsteadiness, and muscular weakness.[71, 74] There is a minimum of drowsiness and lethargy.[21]

Benactyzine

Benactyzine (Suavitil) is a mild neurosedative effective chiefly in anxiety and tension states. About 68% of 40 such cases responded favourably to the drug in the experiences of Raymond[75] and Davies.[76] There have also been encouraging preliminary results in the treatment of psychosomatic illnesses and obsessive-compulsion neurosis, but hysteria and neurotic depression were not diminished.[75, 76]

Coady[77] found no evidence of decrease in muscular rigidity in 80 neurological cases receiving benactyzine therapy. In psychoses, results were generally poor.[78] However, Davies[76] observed improvement in 11 of 14 depressed patients.

No toxic effects were reported in 190 patients.[76, 77] Side-effects were mild but occurred in about half of two small series.[75, 77] They included heaviness in the limbs, giddiness, ataxia, blurred vision, drowsiness, apathy, increased anxiety, nausea, and diarrhœa.

Azacyclonol

Azacyclonol (Frenquel) is reported to block drug-induced hallucinations[79-81] and has been advocated for the control of hallucinations and delusions in alcoholism, acute schizophrenia, and senile and postoperative toxic confusional states.[9, 78, 82-84]

With azacyclonol therapy, Cohen[85] observed improvement in 35 of 100 psychotic patients (mostly schizophrenics). Results paralleled the patient's behaviour pattern; improvement occurred in most of the disturbed acute and many of the subacute, but in none of the quiet chronic patients. Also, Rudy *et al.*[3] reported benefit in 8 of 17 paranoid patients, and Fabing[78] found it rapidly effective in 5 of 14 acute and only a "few" of 34 chronic schizophrenic patients. Clark[84] and Rosner *et al.*[86] confirm that the drug is not effective in chronic schizophrenia.

Not all agree, however, that azacyclonol benefits psychotic patients or even exerts an antihallucinatory action. In a double-blind study, Clark[84] failed to demonstrate an antihallucinatory effect, and Lemere[87] observed no beneficial effects in 61 patients with hallucinations, delusions, and confusional states. Lastly, Margolis[9] writes that eight respondent investigators found azacyclonol disappointing; three (reporting 180 cases) believed it was effective only in a few toxic states.

The drug appeared to be completely nontoxic in 888 cases.[47, 54, 78, 85, 88] In 10 cases where renal and hepatic functions were studied, no deleterious effects were observed.[85] The side-effects are mini-

mal, and it does not produce hypotension or tend to immobilize patients.

Ethylcrotonyl Urea

Ethylcrotonyl urea (Nostyn) is a mild tranquillizer which was recently reported effective in relieving anxiety and tension in a study by Ferguson.[89] After receiving the medication, 82% of his 106 patients, who were worriers, hypochondriacs, and excitable, flighty persons, seemed more calm. In 27 epileptic patients on phenylhydantoin sodium (Dilantin), seizures were reduced from 65 to 4 per month for the group as a whole, when ethylcrotonyl urea was added. No toxic effects were observed in 142 patients.[89]

Most observers believe that the drug has a mild tension-relieving action; however, few well-controlled investigations have been published. It is not effective in treating psychoses or alcoholism or the extremely hyperactive patient.

Meprobamate

A double-blind technique was utilized by West[90] to test meprobamate (Miltown, Equanil) in 26 patients with anxiety and tension. The patients served as their own controls, and they successfully identified the active drug. In other studies, patients with anxiety and tension states obtained significant relief from their symptoms on meprobamate; the percentages of 1570 patients showing improvement are listed by diagnostic or descriptive categories in Table III.

Nussbaum *et al.*[91] and Dunsmore *et al.*[92] advise that the tranquillizer is no substitute for adequate antihypertensive treatment but is superior to reserpine or phenobarbital as adjunctive therapy for apprehension or headache in hypertensive patients. When meprobamate was given prophylactically to patients with tension headache, 65% of 150 benefited, compared with a 46% placebo response, whereas the incidence of migraine headaches was not significantly reduced in 60 patients.[107]

Only about half of patients with psychoneurosis (type unspecified) or hysteria responded favourably, and even less effect was noted in obsessive compulsion neurosis, phobias, conversion reactions, and reactive depressions. Nonpsychotic behaviour problems, schizophrenia, and endogenous depression likewise failed to respond. At variance with these results and therefore not averaged with them was one report of improvement in 40% of mild schizophrenics on meprobamate.[108]

In the 31 articles on meprobamate reviewed (representing over 3000 patients), 29 serious reactions were mentioned. Their actual incidence cannot be determined but is low. There were 25 allergic skin reactions, consisting principally in erythema or urticaria, pruritus, œdema, fever, and sometimes vascular collapse. There were two addictions with toxic withdrawal phases[109] and two severe gastro-intestinal complaints.[93, 110]

TABLE III.—THE PERCENTAGES OF 1570 PATIENTS SHOWING IMPROVEMENT (CUMULATED DATA) ON MEPROBAMATE, IN DESCENDING ORDER OF EFFECTIVENESS

Diagnostic or descriptive category	*Number patients treated*	*Per cent of patients improved*	*Authors*
Headache and apprehension in hypertensives	58	93	91, 92
Tension headaches	104	86	93
Motion sickness	29	86	93
Idiopathic petit mal	18	83	94
Muscle spasm	203	76	95, 96
Emotional instability	49	72	93
Alcoholism	124	69	97, 98, 99, 100
Anxiety or tension states	383	69	90, 97, 98, 99, 101, 102
Organic brain syndrome	28	64	97, 98, 102, 103
Senile psychosis	20	55	104
Hysteria	32	50	90, 98
Psychoneurosis (type unspecified)	38	48	97, 102, 103
Psychopathic personality	25	48	90, 94, 98, 101
Obsessive compulsions	29	47	90, 97, 99, 101
Involutional depression	71	44	90, 97, 98, 99, 101, 102
Reactive depression	56	41	90, 98, 101, 102, 105
Psychosomatic problems	83	38	18
Nonpsychotic behaviour problems	32	38	94, 98
Schizophrenia	175	33	90, 97, 98, 99, 101, 102, 106, 108
Epilepsy	76	24	94, 103
Cerebral palsy	44	23	94

The side-effects of the drug are minor and most are uncommon. Drowsiness in some degree occurs in one-third to one-half of patients. Other effects are morbilliform rash, dizziness, headache, paradoxical excitement, nausea or gastric discomfort, and exacerbation of grand mal epilepsy. About two-thirds of the side-effects can be controlled by reducing the dosage by half.[95]

In 50 normal subjects given meprobamate, careful studies revealed no deterioration in motor skills or mental performance.[111]

Phenaglycodol

The calming effect of phenaglycodol (Acalo or, in the U.S., Ultran) was first observed in humans during a study of its antiepileptic qualities.[112] (A moderate antiepileptic effect was demonstrated in petit mal and epilepsy associated with focal brain damage.)[113] But the important tranquillizing action is more difficult to measure. On a closed psychiatric ward, where noisy, aggressive patients require potent sedatives with antipsychotic actions, one can determine the noise level in decibels or the average life-span of water pitchers and flower vases; however, in ambulatory, nonpsychotic candidates for mild tranquillizers, the double-blind technique is essential to demonstrate activity of the drug beyond the placebo effect of an inert pill.

This technique was used by Martz[114] to test phenaglycodol in 30 patients with mild anxiety, and the results clearly showed its activity. Good or excellent results were reported by Denyse[115]

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in 73% of 111 hypertensive patients with anxiety or tension states and by Settel[116] in 75% of 67 agitated senile patients. Extremely agitated and psychotic patients benefited least. In a preliminary report, Samuels[117] states that phenaglycodol increased the walking ability and decreased muscle cramping in 20 patients with arteriosclerosis obliterans and intermittent claudication.

The effectiveness of phenaglycodol in controlling anxiety and tension states, as reported in an extended clinical trial investigation, is shown in Table IV. The percentages of 4860 patients who improved are listed by diagnostic or descriptive categories.

TABLE IV.—THE PERCENTAGES OF 4860 PATIENTS SHOWING IMPROVEMENT ON PHENAGLYCODOL, IN DESCENDING ORDER OF EFFECTIVENESS[118]

Diagnostic or descriptive category	*Number patients treated*	*Per cent of patients improved*
Premenstrual tension	77	86
Insomnia or somnambulism	49	82
Neurasthenia and neurocirculatory asthenia	105	75
Emotional instability	55	75
Menopause	475	74
Anxiety states	2719	72
Pain (adjunct)	48	71
Psychosomatic illnesses	380	71
Alcoholism	109	71
Tension headache	116	69
Migraine headache	46	63
Hysteria	68	63
Psychoneurosis (type unspecified)	238	62
Senile agitated	46	61
Reactive depression	238	57
Schizophrenia	23	52
Paralysis agitans	26	50
Epilepsy	21	48
Hypochondria	21	20

Seventy-two per cent of 2719 cases designated anxiety states responded well. In other conditions characterized by chronic anxiety, emotional tension, or psychic fatigue, improvement occurred in 71 to 86% of patients with premenstrual tension, insomnia, neurasthenia, emotional instability, menopause, pain, psychosomatic illnesses (asthma, hay fever, dermatoses, gastro-intestinal complaints), and alcoholism.

In reports from 383 physicians[118] (representing 6806 patients), no serious toxic reactions were mentioned. Side-effects were reported as follows: drowsiness 2.3%; nausea, gastric distress, and disequilibrium—each 1%; dermatitis 0.4%; depression and anxiety 0.28%; and headache 0.25%. Other side-effects which occurred in less than 0.15% of cases included feelings of unreality, lethargy and insomnia, and gynæcomastia.

Reitan[119] utilized a battery of psychological tests in an interesting study on the effect of phenaglycodol and meprobamate on alertness, attention, and reaction time. No deleterious effect of either drug was observed on these functions.

DISCUSSION AND CONCLUSIONS

In examining the current status of the tranquillizers, the data of various observers were cumulated into diagnostic or descriptive categories and presented in terms of the percentage of patients showing moderate or better improvement and the incidence of toxic reactions and side-effects.

Because this is only one approach to the problem, the meaning of specific results must be left to the reader's judgment. However, certain general conclusions and impressions seem justified.

1. There are two major types of tranquillizers, or agents that calm with minimal hypnotic action, those with and those without potent antipsychotic effects. The first type quiets violent psychotics and sometimes brings about their return to society. The second may prevent neurotic breakdown in anxious or tense patients under stress and may keep an acute neurosis from becoming chronic.

2. Several of these drugs are as well documented as the familiar barbiturates, and their indications are rapidly being established. Their effectiveness depends greatly upon the care with which they are prescribed because their actions differ widely and patients often respond to one and not another.

3. Tranquillizers do not cure but provide a type of symptomatic relief not previously available which permits the patient to express his emotions more normally (or to suffer less disruptive emotions), and, therefore, to channel his psychic energies more effectively and more in accord with the needs of everyday life.

4. There is a keen point of difference between control of feelings (or their expression as withdrawn or violent behaviour), which are often amenable to drug therapy, and control of thought content, which lies in quite a different province.

5. Tranquillizers offer no substitute for accurate diagnosis or adequate medical supervision. They are adjuncts, likely to displace but not entirely replace some of the older therapies. Thus, the severely depressed patient may require insulin coma or electroconvulsive therapy, and a few lobotomies may still be necessary. Psychotherapy remains an important tool, and tranquillizers can increase its effectiveness by improving rapport with the patient.

6. All things considered, the new drugs are safe. Toxic reactions are rare. The numerous side-effects are seldom dangerous and not more common than is expected of pharmacologically active agents.

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Association Notes

THE 91ST ANNUAL MEETING

If you plan to combine pleasure with education next June, the following account of New Brunswick pleasures (prepared by the N.B. Tourist Bureau, Fredericton) will help you. Our Annual Meeting is not far from the places described, for it will take place in Halifax, N.S., from June 16 to June 20.

TOURING NEW BRUNSWICK

The world's finest salmon fishing, handicrafts, scenery, sports, historic interest and natural phenomena are well blended in New Brunswick—Canada's "Picture Province"—which usually is at its very loveliest during the month of June.

The greens of the rolling hills, the thick evergreen forests and grassy slopes are at their prettiest throughout all of the province's 28,000 square miles.

New Brunswick is a province to "explore"—it has as many hidden charms as it has more obvious ones. There are 600 miles of coast-line, bringing the lure of the sea to delight and fascinate inland dwellers. The coasts offer you their gifts of driftwood—yours for the choosing—and the pleasure of strolling among sun-lit beaches while the Atlantic rolls in over golden sand to bid you welcome.

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N.B. Travel Bureau Photo

WELLS IN THE ROCKS, at Grand Falls, New Brunswick. Giant kettles scooped out of solid rock, which annually attract camera fans and tourists to see this quirk of nature.

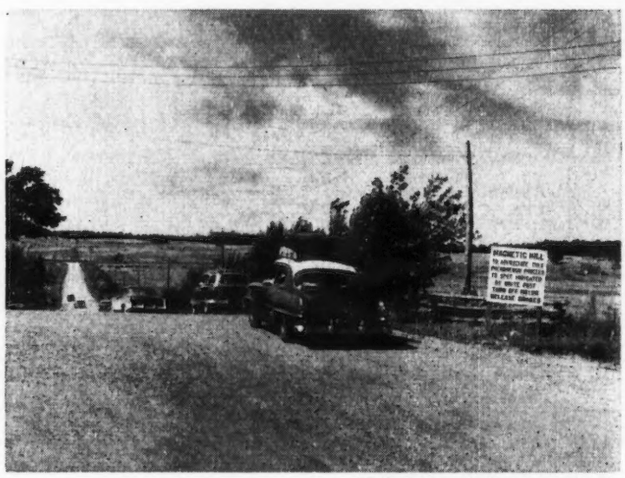
June in New Brunswick offers you long, warm days beside the many beautiful rivers. The Saint John river is "The Rhine of America"—and when you visit it, be sure to have a camera handy. Of this river valley, the noted author, Nicholas Monsarrat—of "The Cruel Sea" fame—has said: "The road follows the river, and the river, treelined, broadening here and there to a noble width, ran through notably attractive country. There was rich farming land; there was hay-making; there were apple orchards; there was, for mile after mile, the river to be enjoyed, bridges to be crossed and re-crossed, steep slopes to be negotiated. This is surely one of the show-pieces of eastern Canada, deserving far greater renown than it now enjoys; indeed, there are many scenic drives in southern France and Italy which have attained world fame on far more slender assets."

New Brunswick invites you to spend your vacation within its borders—to take your time in discovering the many unique quirks of nature.

For instance, there's the famous tidal bore in Moncton, where a solid wall of water rushes from the Bay of Fundy into the confines of the Petitcodiac River. Because the tides of Fundy are the highest in the world, the water gathers itself into a fury to find an outlet for its magnitude.

Near Moncton, at Hopewell, you may also see the fascinating Sentinels, and the Flower Pots. These are unusual rock formations—hewn by the relentless tides of the Atlantic from the soft red sandstone banks. Small bushes and shrubs cling tenaciously to the tops of these rock pillars, prompting Robert Ripley of "Believe It or Not" fame to name them the largest "flower pots" in the world.

Magnetic Hill near Moncton offers another attraction to the visitor. There is also a provincial wildlife farm, where forest animals will eat out of your hand. The Magnetic Hill has puzzled visitors for years—and still does. Apparently, one travels uphill without power; that is, you drive your car to the bottom of the hill—turn off the ignition, put the gears in neutral—and then it happens! The car miraculously travels back "uphill" without power.



N.B. Travel Bureau Photo

MAGNETIC HILL, near Moncton, New Brunswick—where cars back up hill apparently without power. For a weird sensation, for the feeling of complete unreality, try a trip on this puzzling hill. Any suggestions as to "why" will be gratefully received.

N.B. Travel Bureau Photo

FLOWER POTS—the largest in the world, according to Robert Ripley of "Believe It or Not". These large pillars of rocks are at Hopewell, near Moncton, New Brunswick. They were carved by the untiring tides of the Atlantic from the soft red sandstone of the shoreline. The rocks and their strange patterns have brought thousands of tourists to admire this unique attraction.

At Saint John you'll enjoy watching the reversing falls. The falls actually travel back up-river at the turn of the tide, because the rise of the Bay of Fundy is so tremendous that it pushes the usually placid river water back over a rock ledge—and on up-river. The water reaches a tormented fury at the turn of the tide, but at slack tide is as calm as a duck-pond.

At Grand Falls, visit the tremendous waterfall which gave the town its name. Also see the kettles in the rocks—big round cauldrons scooped out of solid rock.

At Woodstock there's harness racing at Island Park. As the name indicates, this Island has been made into one large park and playground—with picnic and barbecue facilities, a swimming pool, and playgrounds for children.

At Hartland, there's the longest covered bridge in the world—1282 feet in length, and a salmon pool which is easily accessible and which offers you excellent fishing.

Fundy National Park, too, will welcome you. It's 80 square miles of natural wonderland—rugged beauty at its best, with all the man-made conveniences to make your trip pleasant. Reservations will rent a chalet-type cottage in the park for you, and inside

N.B. Travel Bureau Photo

SATAN'S STEW POT could be another name given to the Reversing Falls at Saint John, New Brunswick. The spectacle can be seen daily from the Reversing Falls Tourist Bureau, which is built on a rocky ledge high above the boiling turbulence of the water. The phenomenon is caused when the tidal water of the Bay of Fundy pushes the waters of the Saint John River back up-river, over a rocky ledge in the steep gorge.

the boundaries of Fundy, you'll find excellent fishing, boating, swimming in a heated salt-water outdoor pool, and golfing, lawnbowling, tennis and croquet.

The New Brunswick Department of Industry and Development's Handicrafts branch also has a "school" at Fundy, where you may take a few days' course in woodwork, leatherwork, metalcraft, basketry, pottery, furniture upholstery, weaving or rug hooking. Trained instructors are supplied by the provincial government to help you in your projects.

Saint John offers much to charm the visitor—with its ancient city market, martello tower and the doll museum, the Provincial Museum, and King Square of Loyalist fame. New Brunswick is a province you'll love—and June is the best month to see it.

New Brunswick Travel Bureau,
Fredericton, N.B.

THE LONDON LETTER

(From our own correspondent)

The Minister Reports

The recently published annual report of the Minister of Health for 1956 records the steadily increasing cost of the National Health Service—an increase in the year of £40 million, which brings the total cost for England and Wales to around £535 million. Practically all branches of the Service participate in this increase, including the cost of drugs, which now amounts to £56.9 million, with an average cost per prescription of about 59.56d. (about 70 cents). An interesting feature of the drug bill is that, whilst antibiotics accounted for only 6.8% of the drugs dispensed by pharmacists for doctors, they accounted for 20.6% of the net ingredient cost of prescriptions. Cough preparations, on the other hand, accounted for 12.4% of prescriptions, but only 5.8% of their cost.

The statistics for general practice throw an interesting light on the way things are moving in this vital section of the Service. Since 1952 the number of single-handed practitioners has decreased by 12.4%—from 7459 to 6568, whilst the number of partnerships has increased. The number of principals in partnership has risen in the same period from 9745 to 12,514. Two-men partnerships are still the most common, but there are now 333 partnerships of six doctors or more. There is still no evidence of general practitioners being able, or willing, to retire at around the conventional retiring age, and in 1956 there were 1263 doctors aged 66 years or over in general practice. A figure which is bound to arouse particular interest in North America is the number of general practitioners in the Service who attended a refresher course in the year—1683. (The number of principals providing unrestricted medical services in 1956 was 19,082.)

New Chair of Rheumatology

The senate of the University of London has instituted a chair of rheumatology to be tenable at the Postgraduate Medical School, Hammersmith. This is only the second chair of rheumatology in this country, and both have been endowed by the Empire Rheumatism Council. The other one, which was founded several years ago, is at the University of Manchester. There are, of course, active departments of rheumatology in several universities, but by no means in as many as there might be. The Empire Rheumatism Council has rightly decided that the most promising approach to the solution of the problem of the rheumatic diseases is to concentrate on the unsolved fundamental problems, and the solution to these is most likely to be found by planned research carried out in active university departments, working in close association with the clinical facilities available in the area.

Association of Anæsthetists

The annual meeting of the Association of Anæsthetists of Great Britain and Ireland last month was of especial interest as it marked the silver jubilee of the foundation of the Association—in 1932. Some 500 anæsthetists attended the meeting—an all-time record—and there was a most satisfactory representation from abroad. The Association has every reason to look back with pride upon the progress achieved during this quarter of a century. During this period three university chairs of anæsthesia have been founded, and since the inauguration of the National Health Service there has been a 60% increase in the number of consultant anæsthetists.

Doctors' Gift to Lord Nuffield

A pleasing ceremony took place at Cowley, Oxford, a few days before Christmas when, on behalf of doctors all over the world, three leaders of the profession presented to Lord Nuffield a pair of diamond cuff links and a cheque for £3,500, in the hope that he would spend it in some way "which would keep him in mind of the regard for him which it betokens". The occasion was Lord Nuffield's 80th birthday, and the gift is an expression on the part of the profession for all that he has done for medicine during the last 20 to 30 years. The three members of the profession

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who presented the gifts were Sir Clement Price Thomas, the president of the Royal Society of Medicine, Sir Henry Dale, the Grand Old Man of medical research, and Dr. William Pickles, the Grand Old Man of general practice.

PRINCESS MARGARET

On December 11, Princess Margaret was admitted to honorary fellowship of the Royal Society of Medicine. The occasion was a pleasantly informal one, attended only by members of the council of the Society. Her Royal Highness was presented by Lord Evans, and the diploma was presented to her by Sir Clement Price Thomas, the president of the Society.

London, January 1958. WILLIAM A. R. THOMSON

ABSTRACTS *from current literature*

MEDICINE

Varied Clinical Manifestations of Pulmonary Embolism.

H. L. ISRAEL AND F. GOLDSTEIN: *Ann. Int. Med.*, 47: 202, 1957.

In this paper, the writers submit that pulmonary embolism has become the most common disease of the lungs encountered in general hospitals. Ninety instances were recognized in an 18-month period in one general hospital, outnumbering pneumonia and bronchogenic carcinoma. Embolism was preceded by surgery in 33 patients, and by musculoskeletal trauma in six. Embolism occurred in 18 patients hospitalized with medical illnesses. In 33 instances, embolism occurred prior to admission to hospital. Respiratory symptoms predominated in 39 instances, cardiovascular in 33. Abdominal symptoms were most prominent in six patients, and central nervous system manifestations in four. The disease most often requiring differentiation from embolism was acute myocardial infarction.

Chest roentgenograms were important in the diagnosis of pulmonary embolism. There was no pathognomonic configuration, but as the x-ray department became more alert to the characteristic features of infarction, this possibility was suspected in 55.2% of patients with pulmonary embolism who were x-rayed. Electrocardiographic abnormalities were detected in 70% of cases adequately examined. Typical cor pulmonale patterns were observed in seven patients, transient positional changes in 28, and coronary insufficiency patterns in 18. The high frequency of transient electrocardiographic changes observed is remarkable since the episodes of embolism were so often of moderate or slight severity. Serum glutamic oxalacetic transaminase determinations were made in 49 patients. Levels were consistently normal in 32 patients, while elevations were noted in 17 patients. In all but one of these, associated hepatic, myocardial or musculoskeletal disease accounted for the elevation. In the absence of these complicating factors, transaminase determinations are valuable in differentiation of pulmonary and myocardial infarction.

The writers consider that pulmonary embolism will be more commonly recognized when it is appreciated as being the most common lung disease now encountered in general hospitals, when this diagnosis is given first consideration in a wide variety of syndromes, and when informed use is made of chest roentgenograms, electrocardiograms, and serum transaminase determinations. S. J. SHANE

Patent Ductus Arteriosus with Pulmonary Hypertension: Temporary Obstruction of the Ductus During Cardiac Catheterization to Evaluate Indication for Surgical Closure.

P. KEZDI *et al.*: *Dis. Chest*, 32: 315, 1957.

It has been suggested in recent reports that a patent ductus arteriosus with pulmonary hypertension and partial reversal of the shunt may be closed if special precautions are undertaken during surgery. In children the results seem to be more promising than in adults. Based on experience with a limited number of cases, the consensus is that closure of the ductus may be hazardous if, preoperatively, a right-to-left shunt can be demonstrated which exceeds the magnitude of the left-to-right shunt. However, the calculation of shunts using the Fick principle in the presence of bidirectional flow through the ductus is far from accurate.

This report illustrates the possibility of prediction of the changes in pulmonary artery pressure and of a more accurate calculation of the shunts without surgical exploration. The ductus can be occluded during cardiac catheterization by a special three-way catheter with an inflatable balloon attachment which is placed in the patent ductus. The danger of the procedure does not exceed that of the usual cardiac catheterization, and it may avoid an unnecessary thoracotomy. S. J. SHANE

U.S. Veterans Administration—Armed Forces Cooperative Studies of Tuberculosis. VI. Survival among Patients with Miliary and Meningeal Tuberculosis (1948-1955).

J. H. WILLIAMS, JR.: *Am. Rev. Tuberc.*, 76: 360, 1957.

The survival rate of 772 patients with miliary, meningeal or miliary and meningeal tuberculosis treated in hospitals participating in a co-operative study of the chemotherapy of tuberculosis was determined for different types of antimicrobial agents including isoniazid-streptomycin, most often with PAS in addition. Since the introduction of isoniazid in 1952, the estimated survival rate at two years after the start of therapy for miliary tuberculosis was 95%; for meningeal tuberculosis, 80%; and for miliary and meningeal tuberculosis, 77%.

The addition of isoniazid to the therapy of miliary tuberculosis has been effective in lowering the incidence of meningitis among patients with miliary tuberculosis. Increasing age decreased the probability of survival for miliary and meningitic patients. The incidence of miliary and of meningeal tuberculosis was higher among non-whites than among whites. This was evidenced by the fact that, while non-whites constitute approximately one-tenth of the veteran population, nearly one-half of the patients reported in the present study were non-white veterans. However, race was not an important consideration in the survival of treated patients.

Premature or irregular discharge resulted in an increase in the probability of death among patients with tuberculous meningitis. S. J. SHANE

SURGERY

Serum Amylase Test in Differential Diagnosis of Freely Perforated Ulcer and Acute Pancreatitis.

S. A. ROSENBURG AND S. AKGUN: *A.M.A. Arch. Surg.*, 75: 41, 1957.

Since perforated peptic ulcer is best treated by early surgical closure of the perforation and acute pancreatitis is best treated by non-operative means, a test that helps to differentiate between the two is of great value. Generally, a value for serum amylase, taken within 48 hours of the onset, that is in the neighbourhood of 1000 Somogyi units points to a diagnosis of acute pancreatitis. However, two cases of perforated ulcer, both large, showed such a rise in serum amylase value and neither showed free air in the peritoneal cavity on x-ray examination. In animals, injection of duodenal juices into the peritoneal cavity caused a high serum amylase value, as does the injection of morphine.

Withholding operation on the evidence of a high serum amylase value may prove fatal in the case of perforated ulcer. It is suggested that peritoneal aspiration might solve the dilemma when the clinical diagnosis is in doubt after clinical and other examinations.

BURNS PLEWES

Carcinoma of the Rectum and Pregnancy.

R. P. WARREN: *Brit. J. Surg.*, 45: 61, 1957.

During 25 years, 1600 women were treated for carcinoma of the rectum; 108 were aged 40 or under, and nine of these were pregnant. In six of the latter a radical excision of the rectum was done; a palliative operation was performed in the other three, who had metastases in the liver.

The rectum should be excised after parturition if the diagnosis is made in the last two months; Cæsarean section before term seems best since it avoids dystocia, lessens the risk of embolic metastases and permits examination of the peritoneal cavity to determine operability. Diagnosis of the carcinoma earlier poses the question whether pregnancy adversely affects the prognosis; the enlarged uterus may hinder the operative procedure, or abortion may complicate postoperative convalescence.

Available data show no evidence that pregnancy has an adverse effect on carcinoma of the rectum. The gravid uterus even at six months does not make excision of the rectum more difficult. The possible ill-effects of spontaneous abortion are not sufficient reason to delay the operation. There seems no good reason to terminate the pregnancy because of the finding of a cancer of the rectum except when postoperative infection is anticipated.

Five of these nine persons survived five years. Three patients who had excision of the rectum for carcinoma had children afterwards. Patients who have survived five years after treatment for rectal cancer need not be advised against pregnancy for medical reasons.

BURNS PLEWES

Polyps of the Colon in Children.

D. L. GORDON *et al.*: *A.M.A. Arch. Surg.*, 75: 90, 1957.

At the Mayo Clinic the incidence of polyposis of the colon in children under 15 is 1 in 1500. Rectal loss of bright red blood was the presenting sign in 99 out of 104 cases; the rest were found on routine examination. Other signs and symptoms were mucus in the stools, abdominal cramps, vomiting, diarrhœa and, in a few cases, passage of fleshy masses per rectum. Rectal polyps were palpable on digital examination in 17 cases. The youngest patient was 13 months old. In 75% sigmoidoscopic examinations and in 66% roentgenograms showed colonic polyps. In 51% of cases of children with fewer than 10 polyps, all polyps were within 24 cm. of the anal verge and therefore could be treated by fulgurization.

In all cases, removal of the polyps was advised. If the polyps were within reach of the sigmoidoscope they were fulgurated. Others were removed by the transcolonic approach. Resection of a segment of colon was performed twice and ileosigmoidostomy was carried out six times.

In many patients follow-up revealed more polyps which had to be removed. Some children have diffuse polyposis, not always familial; if this is left untreated it will certainly develop into carcinoma of the colon. The prognosis in children with a single polyp or only a few polyps removed is not known, but a few are destined to develop diffuse polyposis. The problems and disability of an ileostomy are real; it is best to perform subtotal colectomy and rely on regular proctoscopic examinations and fulguration to control lesions in the remaining rectosigmoid. Colectomy should be done if more than five or six polyps are found scattered throughout the bowel. But there is time for repeated evaluations, for carcinoma is rare before puberty but becomes frequent between 16 and 20 years in multiple polyposis.

BURNS PLEWES

THERAPEUTICS

Treatment of Hyperthyroidism with I^{131}.

R. E. BECK AND A. A. HOBBS, JR.: *Ann. Int. Med.*, 47: 241, 1957.

Radioactive iodine has not been universally accepted as the therapeutic agent for all cases of hyperthyroidism. The authors used it in the treatment of 106 hyperthyroid patients who were completely unselected except that pregnant women were not included. The majority of patients treated were adult females, but 39% were less than 40 years of age, and 6% were children.

The objective was to administer a single curative dose based on the weight of the thyroid gland and its capacity to accept I^{131}. The weight of the thyroid gland was calculated from scintillograms.

The results were based on a median post-treatment period of 14 months. In 93% of patients the hyperthyroidism was effectively regulated, including seven patients who became permanently hypothyroid. In 88 cases classified as diffuse toxic goitre, there were only three therapeutic failures. In all of these less than 81 μc. of I^{131} per g. of thyroid tissue was administered. Four failures occurred among the 18 cases of nodular toxic goitre; in these, less than 121 μc./g. were administered. No treatment failures occurred in any case in which the dose was more than 120 μc./g. Ninety-three per cent of the patients with definite thyroid enlargement experienced appreciable reductions in thyroid size. Exophthalmos was cured or greatly alleviated in all except two of 40 patients. Complications were few and infrequent.

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In the treatment of Graves' disease, I^{131} is apparently the agent of choice. This form of therapy is free from risk, from expensive hospitalization, and from the inconvenience that characterizes thyroidectomy. Admittedly, nodular goitres require larger doses for comparable effect and do not respond with the same excellent results, but in this category of patients I^{131} therapy is recommended only where surgery is contraindicated.

At this time, within the second decade of the use of I^{131}, there has been no authentic report of malignant disease incident to its use, and the writers do not consider it reasonable to suspect an adverse genetic effect. They believe that the obvious immediate benefits that result from the use of I^{131} outweigh the very remote possibility of induced malignancy of genetic disturbances.

S. J. SHANE

Regional Enteritis. A Study of 38 Patients Treated Medically.

E. R. ENSRUD AND W. G. SAUER: *Proc. Staff Meet. Mayo Clin.*, 32: 395, 1957.

In 38 conservatively treated patients with regional enteritis, the clinical features in descending order of frequency were diarrhœa, loss of weight, episodes of abdominal pain, febrile episodes, gross rectal bleeding, anal fistula and perirectal inflammation, palpable mass in the right lower quadrant of the abdomen, and internal fistula. The duration of symptoms ranged from three months to 20 years and averaged 3.5 years. In 10 patients the symptomatology suggested a sprue-like syndrome, and in eight of these the presence of steatorrhœa was confirmed by laboratory procedures.

In only 14 of 38 patients did x-ray examination with the aid of a barium enema show the changes of regional enteritis. In 11 patients this examination disclosed a normal condition, but did not permit visualization of the terminal part of the ileum, and in 13 it disclosed a normal condition of both the colon and the terminal part of the ileum. In all 35 patients who underwent x-ray examination of the small intestine changes indicative of regional enteritis were seen. Thus, a normal x-ray appearance of the colon does not exclude regional enteritis; x-ray study of the small intestine should be made when the disease is suspected.

Only two of the 38 patients showed progression to involvement of the colon by the inflammatory process.

Of eight patients who received from one to six courses of x-ray therapy two died of the disease but the remaining six said on follow-up that they were in good general health.

According to follow-up reports, 19 of the 38 patients were in good general health, 10 were in fair health, one was a chronic invalid, and eight had died of the disease from 3.5 years to 11.5 years after the onset of symptoms. It is concluded that conservative management of regional enteritis, although nonspecific and supportive, is of definite benefit and deserves a thorough trial unless complications such as obstruction or fistulas are present.

S. J. SHANE

DERMATOLOGY

Dermatomyositis and the Incidence of Associated Malignancy.

C. SHEARD AND P. T. KNOEPFLER: *A.M.A. Arch. Dermat.*, 75: 224, 1957.

Dermatomyositis is classified as one of the collagen diseases. It usually has an acute onset with erythema, œdema of the face and eyelids, and muscular weakness. The erythema is described as being of heliotrope variety. The œdema may involve the extensor aspects of the extremities as well as the face. Muscle weakness may be very marked and may be made manifest by difficulty in swallowing or talking. Laboratory findings are moderate leukocytosis with relative lymphopenia; alterations in the electrocardiogram due to myocardial changes and albuminuria. The disease lasts from three months to three years. Death occurs most frequently during the first year. Diagnosis is difficult, especially from certain forms of scleroderma. With scleroderma the skin is thickened and hard, while with dermatomyositis the skin has a brawny thickening suggestive of œdema.

The authors briefly present 14 cases. Two were in children, and two were of the chronic variety with partial recovery. Six had associated carcinoma of the gastro-intestinal or genital tracts. The authors question the propriety of using the term collagen disease for those cases which appear to be a peculiar manifestation of some internal carcinoma. They also note that scleroderma is rarely, if ever, associated with internal malignancy. ROBERT JACKSON

Solar Dermatitis.

J. H. LAMB, P. E. JONES AND T. B. MAXWELL: *A.M.A. Arch. Dermat.*, 75: 171, 1957.

The authors classify the solar dermatitides into four types: plaque-like, papular or prurigo-like, contact eczematous type, and multiforme type (erythema solare perstans). This paper deals with the difficulty in making a diagnosis of solar dermatitis, the problem of differentiating it from discoid lupus erythematosus and the use of hormones and antimalarial therapy. Solar dermatitis characteristically occurs in summer or with excesses of sunlight in the winter. It is more common in the male and frequently is worse on the left side of the face due to exposure from the driver's seat of motor vehicles. Low sperm counts may occur in the male. The possibility of very severe reactions to ultraviolet testing is noted. Discoid lupus erythematosus is more common in females. There is more atrophy after healing and more plugging and dilatation of follicles. Biopsies from cases of discoid lupus erythematosus almost always show hyperkeratosis with no parakeratosis in liquefaction of the basal layer. These findings are absent in over one-half the cases of solar dermatitis.

The evidence of hormonal inadequacy as a factor in light-sensitive eruptions is reviewed in some detail. The authors use chorionic gondatrophic hormone and testosterone as well as quinacrine or chloroquine in severe cases. In milder cases the antimalarial drugs are used alone. ROBERT JACKSON

OBITUARIES

DR. ARTHUR E. BLACKETT, 65, radiologist at Aberdeen Hospital, died in New Glasgow, N.S., on December 15. Dr. Blackett was born at Glace Bay, N.S., and was educated at Dalhousie University where he graduated in 1915. After graduating he served overseas with the armed forces as a medical officer with the Third Canadian Division, the 90th Field Ambulance stationary hospital and several hospitals in England. On his return to Canada in 1919 he served for a time at the Camp Hill Hospital before moving to New Glasgow where he lived until the time of his death. A member of the active militia between the wars, Dr. Blackett served with various medical units during World War II and organized the 29th Reserve Field Ambulance which he commanded with the rank of Lieutenant-Colonel. In 1940 he became a Fellow of the Royal College of Physicians of Canada and in 1943 he was elected president of the Medical Society of Nova Scotia. He represented Nova Scotia on the executive of the Canadian Medical Association from 1950-1952 and in 1953 was the Canadian Medical Association's representative at the Coronation of Her Majesty Queen Elizabeth II.

Dr. Blackett is survived by his widow and foster daughter.

DR. FORREST LESMERE HILL, aged 84, a well-known physician and surgeon in Cumberland County, N.S., died at his home in Parrsboro on December 10, 1957. He was born at Economy, N.S., and graduated in medicine from Queen's University, Kingston, Ont., in 1897. He practised medicine for more than 60 years in Nova Scotia—in Halifax County, Advocate, Port Grenville and Parrsboro. Dr. Hill retired from practice in 1950.

He is survived by his widow.

DR. HUGH MACLEAN, 79, died at La Jolla, California, on January 1. Dr. MacLean was born in Glasgow, Scotland, and the family emigrated to Marthaville, Ont., in 1887. He received his medical education at the University of Toronto Medical School, graduating in 1906. After graduation he served for a short time at the Gravenhurst, Ont., sanatorium and then moved to Lang, Sask. After doing postgraduate work in Canada and the United States he returned to Regina to commence practice in 1913. During the First World War Dr. MacLean served on the military medical board for Regina, and was recruiting officer for the Cameron Highlanders and medical officer for the 77th Battery. Dr. MacLean was a Fellow of the Royal College of Surgeons of Canada and of the American College of Surgeons.

He is survived by his widow and three daughters.

DR. HUGH MACLEAN

AN APPRECIATION

T.C.R. writes: "Although nearly 20 years have elapsed since Dr. Hugh MacLean of Regina departed from that city in Canada to a more salubrious climate because of his health, he will still be remembered by a great many Canadian members of the medical profession in Canada, particularly the older generation, as one of the stouthearted men of the profession.

"It was my privilege to become acquainted with Dr. MacLean nearly 40 years ago when I first began my activities with organized medicine in Canada. Throughout all the years I knew him, I found him to be a man of the highest principles, a man who could always be counted upon to pull his weight in the boat, and indeed, a man who delighted to spend himself and his substance in the service of others. I remember very vividly in the dark days of the early 1920's, when the Canadian Medical Association faced desperate conditions, indeed, conditions which might have meant the folding up of the Association, that MacLean was amongst that little band of optimists who not only believed in Canada and Canadian medicine, but were determined that the Canadian Medical Association should not fall or fail. He went back from Halifax to his home area of Saskatchewan and busied himself at once in endeavouring to persuade his colleagues to get behind the Canadian Medical Association, and his efforts contributed to a considerable degree in helping to salvage the situation of those days. I shall always remember Hugh MacLean, not only for the contributions he made to organized medicine, but for the unfailing good humour and delightful personality which he brought to every conference or every conclave in which he was engaged. A great man has passed from our midst.

"To Mrs. MacLean and her three daughters, sincere sympathy is extended."

DR. WILLIAM JOHN NICHOLSON, 62, died in Tillsonburg Memorial Hospital on December 2. He was born at Trenton and graduated from Queen's University, Kingston, Ont., in 1922. For the following two years he practised at West Monkton, near Stratford, Ont., and then went to Langton where he practised for 33 years. Dr. Nicholson was a coroner for the County of Norfolk.

He is survived by his widow and two sons.

DR. WILLIAM ALEXANDER ROBERTSON, 75, died at his home in New Westminster, B.C., on December 15, 1957. Dr. Robertson was born in Monkton, Ont., and graduated with an honours degree from the University of Toronto Medical School in 1908. After graduating he practised for a while in Moose Jaw before settling in practice in New Westminster.

Dr. Robertson is survived by his widow, one son and two daughters.

DR. H. A. SMITH, general practitioner and specialist in diseases of eye, ear, nose and throat, died at the General Hospital, St. John's, Newfoundland, on December 7. He was 86 years of age. He was born in North Sydney, N.S., and graduated from Baltimore University, Maryland. He practised for a time on the Southern Shore in Newfoundland and later did postgraduate work in Europe. For many years he was on the staff of the General Hospital at St. John's.

Dr. Smith is survived by his widow and two sons.

DR. WILLIAM JOSEPH TILLMAN, 80, died in St Joseph's Hospital, London, Ont., on December 11. He was born in London and was educated at the University of Western Ontario, London, where he graduated with honours in 1898 and was a gold medallist. After graduating he interned at St. Joseph's and Victoria Hospitals before setting up in private

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practice. Dr. Tillman was a lecturer in chemistry at the Medical School from 1903 to 1909 and from 1909 to 1911 he taught in the department of medicine, rising to the rank of associate professor. He then lectured in pædiatrics and in 1920 became professor. Later he did postgraduate work at the Hospital for Sick Children, Great Ormond Street, London, England. Dr. Tillman was a Fellow of the Royal College of Physicians of Canada, and a member of the British Medical Association. In 1948 the University of Western Ontario awarded him an honorary Doctor of Laws Degree.

Dr. Tillman is survived by his widow, two sons and three daughters.

FORTHCOMING MEETINGS

CANADA

COLLEGE OF GENERAL PRACTICE OF CANADA, Second Scientific Assembly, Winnipeg, Man. (Dr. W. V. Johnston, Executive Director, College of General Practice of Canada, 176 St. George St., Toronto 5, Ont.) April 14-16, 1958.

CANADIAN OTOLARYNGOLOGICAL SOCIETY (SOCIÉTÉ CANADIENNE D'OTOLARYNGOLOGIE), Annual Meeting, Halifax, N.S. (Dr. Donald M. MacRae, 324 Spring Garden Road, Halifax, N.S.) June 9-11, 1958.

CANADIAN TUBERCULOSIS ASSOCIATION, 58th Annual Meeting, Quebec City, P.Q. (Dr. G. J. Wherrett, Executive Secretary, Canadian Tuberculosis Association, 265 Elgin St., Ottawa 4, Ont.) June 9-12, 1958.

CANADIAN MEDICAL ASSOCIATION, 91st Annual Meeting, Halifax, Nova Scotia. (Dr. A. D. Kelly, General Secretary, The Canadian Medical Association, 150 St. George Street, Toronto 5, Ont.) June 15-19, 1958.

INTERNATIONAL FEDERATION OF GYNECOLOGY AND OBSTETRICS, 2nd Congress, Montreal, P.Q. (Professor Léon Gérin-Lajoie, Suite 313, 1414 Drummond Street, Montreal, P.Q.) June 22-28, 1958.

10TH INTERNATIONAL CONGRESS OF GENETICS, Montreal, P.Q. (Mr. J. W. Boyes, General Secretary, 10th International Congress of Genetics, McGill University, Montreal, P.Q.) August 20-27, 1958.

UNITED STATES

AMERICAL COLLEGE OF SURGEONS, Sectional Meeting, New York, N.Y. (Dr. H. P. Saunders, Associate Director, American College of Surgeons.) March 3-6, 1958.

AMERICAN ORTHOPSYCHIATRIC ASSOCIATION, 36th Annual Meeting, New York, N.Y. (Dr. Marion F. Langer, Executive Secretary, American Orthopsychiatric Association, 1790 Broadway, New York 19, N.Y.) March 6-8, 1958.

AMERICAN ACADEMY OF GENERAL PRACTICE, Annual Meeting, Dallas, Texas. (Mr. Mac F. Cahal, Executive Secretary, Volker Boulevard at Brookside, Kansas City 12, Mo.) March 24-27, 1958.

INTERNATIONAL SOCIETY OF GASTROENTEROLOGY, 3rd World Congress, Washington, D.C. (Dr. H. M. Pollard, University Hospital, Ann Arbor, Michigan.) May 25-29, 1958.

OTHER COUNTRIES

FIFTH BAHAMAS MEDICAL CONFERENCE, Nassau, Bahamas. (Dr. B. L. Frank, Organizing Physician, The Dolphin Hotel, Nassau, Bahamas.) April 1-12, 1958.

PROVINCIAL NEWS

ALBERTA

The Alberta Committee on Continuing Medical Education continues to improve the facilities offered to those in practice in the province. At present the activities are confined to three major enterprises:

1. *The Annual Refresher Course.* This is usually held in May and lasts for five days. Of these, two are devoted to medicine, two to surgery, and one to obstetrics. Enrolment is unlimited and the fee is ten dollars.

Dr. Ray Farquharson, Professor of Medicine at the University of Toronto, will be the guest speaker for the medical days. Sir Reginald Watson-Jones had planned to be the surgical speaker but because of an unfortunate injury cannot come. He would have delivered the Fulton Gillespie Memorial Lecture, established in honour of the founder of the Refresher Courses. Dr. Gillespie, then a lecturer in surgery, was chiefly responsible for the first course put on in 1929.

2. *Short Courses.* These last two days, are usually five in number and are conducted during the academic year. Registration is limited to 25 and the fee of $25 includes the cost of luncheons held in conjunction with the courses. For the year 1957-58 the courses are in pædiatrics, endocrinology and metabolism, surgery of trauma (guest speaker, Dr. Dwight Parkinson, Assistant Professor of Surgery, University of Manitoba), obstetrics and gynæcology, and radiology. These courses are usually oversubscribed.

3. *Touring Teams.* The Committee offers the services of touring teams to the various district monthly meetings, hoping to cover two meetings per year in each district. For this purpose, the province is divided into north and south portions with Dr. A. A. Dixon of Calgary handling the south and Dr. R. A. Macbeth of Edmonton looking after the north.

4. *Information.* The committee makes every effort to keep the doctors in the province informed of the visits of prominent doctors to the province in time to enable them to get to the centre where the visitor is speaking.

The Committee on Continuing Medical Education is made up of the Dean's Committee which organizes the refresher courses, plus appointees from the Committee on Education of the Alberta Division of the C. M. A.

At present the Committee is made up of the following members: Chairman, Dr. H. E. Duggan, who is chairman of the Dean's Committee; Secretary, Dr. R. A. Macbeth.

Statutory members of the Dean's Committee: Dr. D. R. Wilson, Professor of Medicine; Dr. W. C. MacKenzie, Professor of Surgery; Dr. J. R. Vant, Professor of Obstetrics and Gynæcology; Dr. W. Bramley-Moore, Secretary, Alberta Division of the Canadian Medical Association; Dr. R. A. MacBeth, Secretary, Committee on Continuing Medical Education.

Members from the Alberta Division, C. M. A.: Dr. A. A. Dixon, Calgary; Dr. G. S. Gray, Lethbridge; Dr. J. A. Weddell, Red Deer; Dr. D. L. McNeil, Calgary; Dr. M. D. Mitchell, Calgary; Dr. J. E. Bradley, Wainwright.

The federal grants to the department of health for raising the standards of laboratory and x-ray services have been apportioned. Hospitals in Calgary and Edmonton have been awarded half of the $400,000 while the remainder has been spread through the province. About $350,000 is to be spent on x-ray equipment while the remainder is to be used in clinical laboratories.

On November 27, Lieutenant-Governor J. J. Bowlan officially opened the new Medicine Hat General Hospital. This unit, which was in construction for two years and cost three and a half million dollars, replaces the first hospital west of Winnipeg which had served up until the present time.

The new hospital includes all the modern equipment for patient comfort, efficient nursing and good medicine and has a capacity of 210. Adjacent to the hospital is a new nurses' home, ranch style in type, air-conditioned, and comfortably finished. W. B. PARSONS

MANITOBA

Dr. J. A. Hildes, Associate Professor, Department of Physiology and Medical Research, University of Manitoba, spoke before the Scientific Club of Winnipeg, December 10, on "Medical Problems in the Arctic". His talk was illustrated with colour photographs which he had taken during his visit to the eastern Arctic regions of Canada.

The Medical Advisory Committee of the Manitoba Sanatorium Board, meeting on November 28, reaffirmed its stand that compulsory chest x-ray examination of School Board employees including teachers should be made effective on a regular basis. It was agreed that routine chest x-ray examination of school children under 15 should be eliminated. Dr. E. L. Ross, Medical Director of the Sanatorium Board, has issued a statement that chest radiography as carried out under the Manitoba Sanatorium Board is safe and necessary.

Dr. R. J. Walton, director of radiotherapy, Winnipeg General Hospital, gave a talk before the Medical History Section of the Winnipeg Medical Society on December 17 on "The History of Radiotherapy". He said that because of the interest taken by so many scientists in the problem of what happens when an electric current passes from anode to cathode in a vacuum tube, Roentgen's discovery in November 1895 was accepted almost at once throughout the civilized world. He stated that it is only within recent years that radiotherapy has become a separate specialty. He referred to radiation agencies now available: x-rays of increasingly higher voltages, radium and radioactive colloidal substances such as cobalt, iodine and gold.

Dr. J. Gordon Hunter of Winnipeg has been appointed senior medical officer for the Canadian National Railways at Vancouver. Graduating in 1942 from the University of Manitoba, he served with the RCAMC from 1943 to 1946; then studied at Deer Lodge Hospital, and later joined the staff of the Winnipeg municipal hospitals. He joined the C.N.R. in 1951 as medical officer in Winnipeg; in 1954 he was classified as a specialist in internal medicine.

Dr. Gordon MacKenzie of Strathclair resigned on September 1 as municipal doctor after serving just over twenty-five years. In November the people of the municipal district gave a surprise party and presented him with a television set and barometer plaque suitably engraved. ROSS MITCHELL

ONTARIO

The March of Dimes has granted $23,984 to the University of Toronto for research at the Connaught Medical Research Laboratories on the food requirements of cultured tissue cells. This cell research grew out of the need to reduce the number of monkeys required from India to make Salk polio vaccine. Virus for Salk vaccine is grown on monkey kidney cells, and since these cells disintegrate as virus is produced, fresh cells from new monkeys are constantly needed to keep vaccine production going. To eliminate the need for thousands of monkeys, workers attempted to develop genetically pure strains of monkey kidney cells which would grow continuously in tissue culture. Another problem arose however. The cultured cells showed marked differences from the original kidney cells from which they were derived. They were no longer susceptible to infection by polio virus, and they contained a different number and kind of chromosomes.

With the new grant, workers hope to determine the essential ingredients in the diet of such cells, which are grown in dialyzed horse serum and a synthetic medium which contains salts, amino acids, vitamins and other nutrients. The work is under the direction of Dr. Angus F. Graham, research associate at Connaught and associate professor of microbiology. Dr. R. B. L. Gwatkin is associated with Dr. Graham in this project.

Dr. George W. Miller, Toronto, national director of the Canadian Red Cross Blood Transfusion Service, accompanied the shipment of Canadian Red Cross relief supplies flown to Ceylon.

Dr. S. J. Klebanoff, of the Rockefeller Institute for Medical Research, addressed the January meeting of the Physiological Society of the University of Toronto on the mechanism of action of ionizing radiations.
LILLIAN A. CHASE

CANADIAN ARMED FORCES

The following officers of the Canadian Armed Forces Medical Services were successful in the recent examinations of the Royal College of Physicians and Surgeons of Canada: Surg. Cdr. R.F. Hand, R.C.N., Ophthalmology, R.C.N. Hospital, Halifax, N.S.; Surg. Cdr. R. H. Roberts, R.C.N., Chief of Medicine, R.C.N. Hospital, Halifax, N.S.; Lt.-Col. A. C. Derby, Fellowship in Surgery; Lt.-Col. L. H. Edwards, Certification in Anæsthesia; Lt.-Col. J. S. Hitsman, Certification in Internal Medicine; Wing Commander E. C. R. Purchase, Certification in Internal Medicine; Wing Commander A. M. Beach, Certification in Psychiatry; Surg. Lcdr. C. A. West, R.C.N., Chief of Medicine, R.C.N. Hospital, Esquimalt, B.C.; Surg. Lcdr. D. W. Brooks, R.C.N., serving on medical staff, R.C.N. Hospital, Halifax, N.S.; Major G. H. D. Evans, Certification in Diagnostic Radiology; Major W. W. Coppinger, Certification in Obstetrics and Gynæcology.

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BOOK REVIEWS

MEDICAL RADIATION BIOLOGY. Friedrich Ellinger, Naval Medical Research Institute, Bethesda, Md. 945 pp. Illust. Charles C Thomas, Springfield, Ill.; The Ryerson Press, Toronto, 1957. $22.00.

Recent developments and applications of nuclear physics have stimulated marked progress in radiobiology and there is a rapidly growing literature involving many different disciplines. Yet, at a time when radiology commands the lively interest and concern of all physicians, a concise presentation by a single author could perform valuable service. Among the few who could attempt such a work, Dr. Ellinger has made an important contribution, particularly for this wide audience. Radiologists and those working in related fields will find stimulating and profitable information less readily accessible elsewhere.

The volume is in textbook form, profusely illustrated by carefully chosen clinical photographs, and is well produced. A thorough introductory table and the arrangement of contents in numbered paragraphs make the absence of an index less inconvenient. There is first an elementary introduction to the physico-chemical interactions of ionizing radiation with living cells. Part two, the largest and most interesting section of the book, is devoted to the appraisal of anatomic and physiologic effects of ionizing radiation on human tissues. The chapter devoted to the effect of radiation on malignant neoplasms is ably done, although it is disappointing to see repeated reference to the "law" of Bergonié and Tribondeau, and the relegation to a footnote of the distinction between radiosensitivity and radiocurability. Total body irradiation is considered concisely, and the radiobiology of internal radiation from radioactive isotopes is summarized in a detailed chapter. Part three deals with the biology of ultraviolet radiation. There is some discussion of the carcinogenic action of ultra-violet light but no adequate description of carcinogenesis resulting from ionizing radiation. The final 244 pages list a large, selective bibliography of international reviews and papers, and the many footnotes give clear, useful information.

The author states his aim as the presentation of the current rationale of ionizing radiation as a therapeutic agent, and of a comprehensive picture of the hazards to health involved in the medical and industrial applications of radiant energy. Those of the medical profession who are confronted by conflicting speculative opinion and unable to pursue the vast literature of radiobiology, will find this book a valuable guide.

CHEMISTRY OF ERYTHROCYTES. Clinical Aspects. H. Behrendt, New York Medical College. 227 pp. Illust. Charles C Thomas, Springfield, Ill.; The Ryerson Press, Toronto, 1957. $6.25.

The chemistry of red blood cells is a subject that belongs primarily to physiologists, and what information is available is widely scattered in the medical literature. In this monograph, Dr. Behrendt has performed a valuable service by assembling the known data within the covers of one book.

The chapter headings are: structure, chemistry, and functional organization; separation of the formed elements of whole blood; hæmoglobin and its derivatives; protein and non-protein nitrogenous substances; carbohydrates; lipids; water and electrolytes; trace elements; enzymes. The material is well organized, and many tables of values are provided. Methods are described only in principle, and not in detail. There is an extensive bibliography and a good index.

ORAL MEDICINE: DIAGNOSIS AND TREATMENT. Lester W. Burket, University of Pennsylvania; with a chapter on Oral Cancer by S. Gordon Castigliano, University of Pennsylvania. 558 pp. Illust. 3rd ed. J. B. Lippincott Company, Montreal, 1957. $15.00.

There are not too many textbooks dealing with the areas of the body of common interest to the dentist and the physician. This book does so, and Dr. Burket is well qualified to integrate the viewpoints of both groups. In the past, many dentists have stressed the restorative phases of clinical practice, but with the growing emphasis on a preventive approach to dentistry it is increasingly important that attention be given to local and systemic diseases affecting the oral cavity over and above those peculiar to the dentition itself. The physician too can broaden his service by familiarizing himself with the numerous manifestations of systemic disturbances appearing in the oral cavity. The patient is bound to benefit from a co-operative service and mutual appreciation of responsibilities. To this effect the author has included sections on gingival disease and intoxications in the mouth, diseases of the tongue and the commoner dermatoses. These are followed by chapters covering the oral aspects of diseases of all the organ systems, as well as those of nutritional and metabolic disturbances, infectious granulomata and occupational hazards in dentistry. A separate chapter on oral cancer written by S. G. Castigliano deals with this problem from the dental point of view. The closing chapters deal with laboratory aids in diagnosis and provide a colour atlas and regional diagnostic indices.

In this new edition the author has revised much of the text, particularly that dealing with treatment, outlining the newer forms of therapy.

MORPHINE AND ALLIED DRUGS. A. K. Reynolds, Department of Pharmacology, Dalhousie University, and Lowell O. Randall. 393 pp. Illust. University of Toronto Press, Toronto, 1957. $10.00.

This is a meticulous review of an extensive literature covering the chemistry, pharmacology and clinical application of these drugs. The problem of addiction and tolerance is discussed at length, and the newer antagonistic chemicals are covered fully. The synthetic analgesics are dealt with somewhat more briefly, and a final summary chapter gives a bird's-eye view of the whole matter.

From a clinician's point of view, the conflict between many of the references cited and the differences between animal and human responses become very confusing, so that the book is not too helpful in settling on a clinical plan of usage. While this is an obvious and inevitable defect of any compendium of reports from the literature, it seems to this reviewer that the authors might with profit have allowed their own opinions on certain matters to shine through, and might have expressed the philosophy of the use of these drugs, especially in chronic situations, a little more emphatically.

As it stands, it is of more value to the pharmacologist than to the practitioner, but it can serve as a valuable source of references to anyone interested in some special aspect of the subject. The book is nicely produced and easy to read.

(Continued on page 226)

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(Continued from page 224)

AN INTRODUCTION TO ELECTROMYOGRAPHY. Fritz Buchthal, University of Copenhagen. 43 pp. Illust. Scandinavian University Books (Gyldendal, Copenhagen; Svenska Bokförlaget/Norstedts, Stockholm; J. W. Cappelen, Oslo), 1957.

This monograph is a chapter from a larger textbook, but its publication as a separate volume is amply justified. It is refreshing to find an author who places electromyography in its proper perspective and states, "If the findings are consistent and interpreted with caution and criticism they may add a valuable stone to the mosaic of findings on which the clinical diagnosis is based."

The book is written to assist the clinician in the understanding and interpretation of the electromyogram. The author discusses briefly the recording systems currently in use and points out the limitations of each. The physiological background is outlined so that the reader may be able to interpret the results intelligently. He does not hesitate to point out the difficulties and confusion that arise frequently, and draws upon his vast experience to support his statements.

This book will prove of value to all who are interested in clinical electromyography.

THE NEW PUBLIC HEALTH: AN INTRODUCTION FOR MIDWIVES, HEALTH VISITORS AND SOCIAL WORKERS. Fred Grundy, Barrister-at-Law, and Professor of Preventive Medicine in the University of Wales. 214 pp. Illust. H. K. Lewis & Co. Ltd., London, 1957. 18s.0d.

As indicated in the subtitle, Dr. Grundy has written this text primarily to meet the needs of student midwives, public health nurses and social workers. It replaces an earlier textbook, "A Handbook of Social Medicine", which was a compilation of lectures given by Dr. Grundy to pupil midwives. This new book serves much the same purpose. Information is compiled in a manner facilitating quick and easy reference, and there are useful diagrammatic charts, tables and other illustrative material of interest.

The first six chapters deal with the organization and administration of the health services in Great Britain and explain the legislation underlying these services. The responsibility of local and national governments is discussed, and the activities of health, education, and welfare authorities are outlined. One chapter is devoted to midwifery. In it the author discusses the various Midwives Acts, and the practice in Great Britain in relation to the care of mothers during the maternity cycle.

The latter four chapters deal with current health needs, with emphasis upon those of concern to midwives and public health nurses. The chapter on the prevention and control of infectious diseases deals primarily with infections of the mother at confinement and of the newborn infant. "The arithmetic of health and disease" is the title of a brief illustrated discussion of statistical methods, centring around maternal and infant mortality. Some consideration is given to the influence of social environment on health, and the concept of "social medicine". A final chapter deals somewhat briefly with a miscellaneous collection of topics including illegitimacy, adoption, abortion, and child protection.

This book presents in a simple and concise form certain aspects of public health in Great Britain. It is no doubt a helpful text for the students for whom it has been written, but its usefulness for a comparable group of students in Canada would be limited.

DIE GERINNUNGSVERHALTNISSE BEI DER SCHWANGEREN UND BEIM NEUGEBORENEN (Clotting Conditions during Pregnancy and in the Newborn). F. K. Beller, Giessen, W. Germany. 171 pp. Illust. Johann Ambrosius Barth Company, Leipzig, W. Germany, 1957. D.M. 22.00.

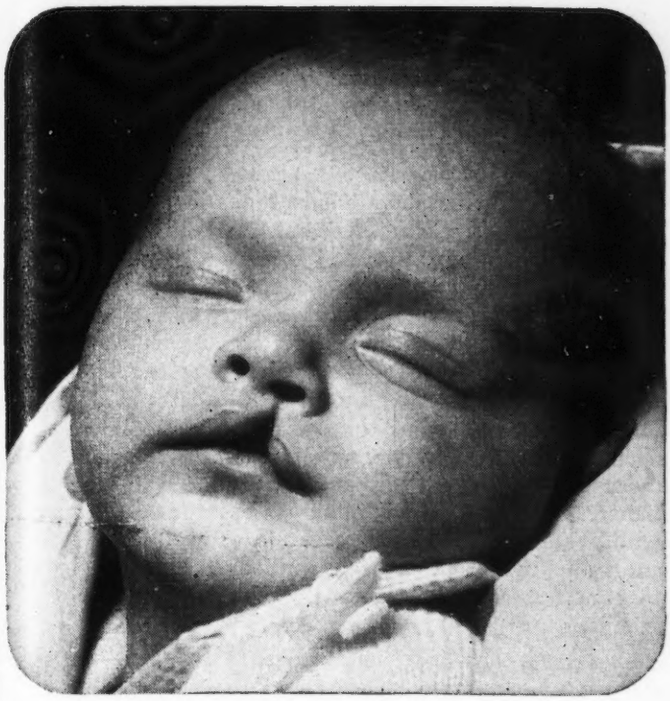
Among the many research developments in the physiology of clotting, little attention has been paid to the special conditions governing clotting during pregnancy and in the newborn. The present monograph represents an attempt to bring together in one volume a survey of the literature and of personal research on the behaviour of the various clotting factors in pregnancy, in labour, in umbilical vein blood, in the puerperium and in the newborn. The material in this book emphasizes once more that clotting conditions are present in the newborn and in late pregnancy which are otherwise found only in pathological circumstances. The explanation is quite unknown, but this monograph may serve as a basis for further research by obstetricians, pædiatricians, and physiologists.

THE DEVELOPMENT AND DISORDERS OF SPEECH IN CHILDHOOD. Muriel E. Morley, United Newcastle-upon-Tyne Teaching Hospitals and Newcastle-upon-Tyne Hospital Management Committee Group. 440 pp. Illust. E. & S. Livingstone Ltd., Edinburgh and London; The Macmillan Company of Canada Limited, Toronto, 1957. $7.65.

This is one of the better speech pathology textbooks covering not only normal speech and language development but also their disorders, such as aphasia, anarthria, dyslalia, and stuttering. It is a textbook for advanced students and will be a valuable aid for the general practitioner. The author is to be congratulated in striking a literary style that makes for particularly pleasant reading in a difficult subject where other authors tend to throw up a "smoke screen" of technical jargon and turgid composition.

The introduction emphasizes so well the necessity in speech therapy for "treating the patient as a whole" and it is therefore perhaps particularly disappointing to find that the publication is so organically oriented that emotional factors are minimized if not entirely ignored. This is a pity because, when such a socially vital function as speech is disturbed, emotional factors are obviously of major importance whether of primary or secondary etiological significance. Another general criticism would be that the work is inadequate in considering treatment techniques for most of the disorders, although in fairness to the author it should be stated that she obviously did not intend it as a handbook for treatment. The section on stuttering is particularly weak in its attempt to reconcile two directly opposed philosophies in terms of the rather archaic and generally disproved approach through "relaxation" and the more contemporary and, we might add, "scientific" approach of learning theory.

(Continued on page 228)



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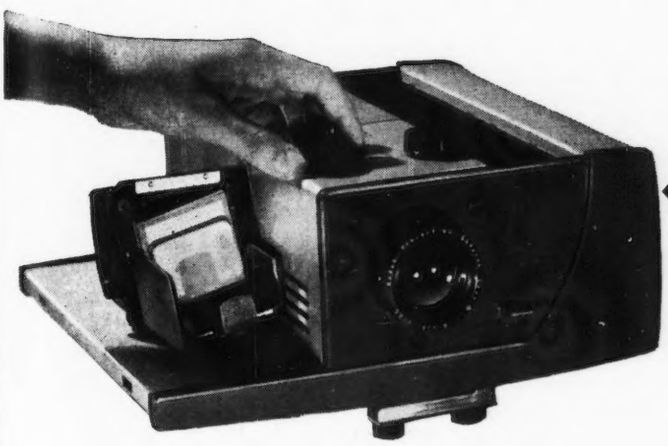

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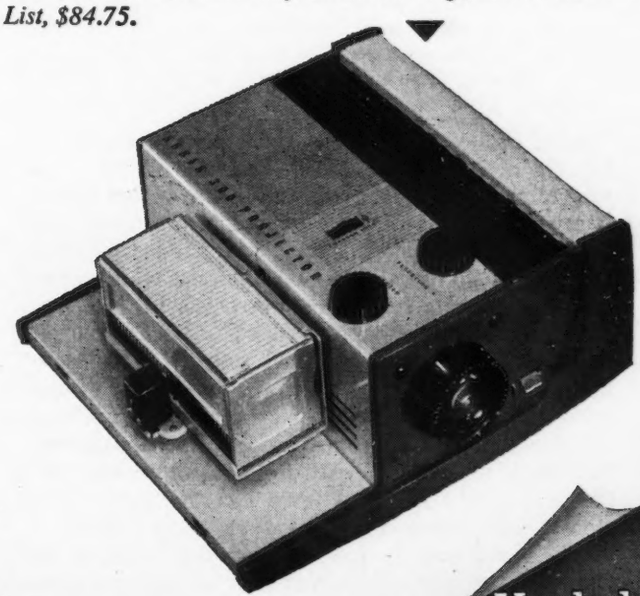

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The work has its limitations but it is still to be recommended as one of the best recently published textbooks, and it will have a particular appeal for the medical man who feels the need to increase his diagnostic knowledge in the field of speech disorders.

HEALTH AND HYGIENE. A. Leslie Banks and J. A. Hislop, Barristers-at-Law, from the Department of Human Ecology, University of Cambridge. 322 pp. Illust. University Tutorial Press Ltd., London, 1957. 15s.0d.

As the authors point out, this book was written to meet the changing emphases in public health: the biological and social environments are recognized now to be of equal importance to the physical environment in affecting man's well-being.

The opening chapters provide an interesting survey account of disease from ancient times to the present day. The different means of disease causation are discussed. This is followed by a section on the control and prevention of infectious diseases. The importance of vital statistics is stressed in understanding health problems and in assessing progress in meeting them. Then follow a group of chapters on man's environment: air and its pollution, climate, nutrition, food preparation and preservation, water, waste disposal, housing, lighting, noise, and other factors are discussed in some detail. The final sections are devoted to the development and organization of the varying "health" services available in the United Kingdom. This section will be of most worth to those interested in public health administration in Great Britain. The last chapter is on international health.

The content of the book is such that its most useful purpose will be as a reference for students and doctors who are interested in the influence of the environment on man's health or ill-health. It is written with thoroughness, conciseness, and clarity, virtues all too rarely found in books today. It is moreover, a book which invites reading.

FINAL REPORT. Research Project for the Study and Treatment of Persons Convicted of Crimes Involving Sexual Aberrations. June 1952 to June 1955. Bernard C. Glueck, Jr., University of Minnesota Medical School, Director. 401 pp. Illust. New York State.

During the past few years there have been several reports of studies of sexual deviation. It is necessary to exercise care in comparing the various reports because of substantial differences in the nature and extent of the studies. Previous reports from New Jersey and California contain findings which differ in some respects from those reported, in this book, of a research study in New York State. For example, the New York report (page v) states: "The current findings confirm the previous ones of a high recidivist rate, with 46.5% of our group having been convicted of at least one previous sexual offense." This high recidivist rate is probably due to the fact that the study is based upon examination of men who were serving a sentence of imprisonment. A much lower rate is found in studies such as the California project, which included less serious cases.

The report is a valuable addition to the researches in sexual deviation.

DIE PATHOLOGIE DES KINDLICHEN PANKREAS (Pathology of the Pancreas in the Child). Gerhard Seifert, Leipzig, Germany. 151 pp. Illust. Georg Thieme Company, Leipzig, Germany, 1956. D.M.-52.00.

The book is an excellent monograph on a subject which in the past has received relatively little attention. It is written by an experienced pathologist and is based on a large collection of autopsy material from more than 500 cases.

First a description is given of the histology and physiological functions of the normal pancreas from fetal life over the newborn period to later childhood. In the following chapters the pathological changes produced by primary diseases of the pancreas are presented; also those produced in the pancreas secondary to other diseases are dealt with in great detail. The exocrine as well as the endocrine tissues have been studied carefully and the findings are illustrated with many photomicrographs.

The book has two very valuable features—an extensive bibliography which includes practically all pertinent publications which have appeared throughout the world; and the integration of morphological findings from physiological and clinical aspects which aid the reader in sharing the author's keen interest in the relationship between structure and function.

The text will be found valuable by students of the subject at any level.

CHIRURGISCHE INDIKATIONEN (Indications for Operation). In honour of Rudolf Nissen's 60th birthday. 299 pp. Illust. Georg Thieme Verlag, Stuttgart; Intercontinental Medical Book Corporation, New York, 1956. $11.00.

Professor Nissen is one of the outstanding surgeons of our generation, and his contributions to surgical literature cover a wide field. He is the author of numerous articles, monographs, and books dealing with general pathology and gastro-intestinal, thoracic and orthopædic surgery. He received his surgical training under Sauerbruch and he was his best-liked pupil, and later his most valued assistant and associate. By 1933 he had left Germany and accepted an invitation to become Professor of Surgery at the University of Istanbul. In 1939, as a research fellow he came to the United States, where he was soon offered a teaching position in New York. In 1952 he returned to Europe to work at the University of Basel, where he is now Professor of Surgery.

Professor Nissen is a true general surgeon, yet no doubt because of the influence of his teacher he leans strongly towards thoracic surgery, and has the distinction of having performed the first successful total pneumonectomy. His friends are many, and under his guidance Basel became one of the important surgical centres of the Continent.

Among the contributors to this book we find the names of Brunner, Mason, Dogliotti, Iselin, Lebsche, Mandl and many more, each contributing a valuable article well representing modern thought and progress in the whole field of general surgery.

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MEDICAL NEWS *in brief*

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DIAGNOSTIC AND PHYSIOLOGIC MEASUREMENTS WITH LEFT HEART CATHETERIZATION

A method for catheterization of the left side of the heart is presented by Blakemore *et al.* (*J. Thoracic Surg.*, 34: 436, 1957). With this method it is possible to obtain simultaneous measurements of pressure in the left atrium, left ventricle and aorta and to obtain indicator dilution (dye) curves from various injection and sampling sites in the left side of the heart or the large arteries. From these measurements, aortic and mitral transvalvular pressure gradients and forward and regurgitant blood flow and left atrial, ventricular and aortic volumes can be determined. When used with proper hydraulic formulas, an estimation of valve orifice area can be calculated with these data. It appears that in patients with aortic stenosis, mitral stenosis, and mitral insufficiency correct diagnosis of the anatomic lesions present and their severity can be made consistently. Methods for evaluating aortic insufficiency are under study. The possibility of serious complications from this technique, although slight, and the ability of the experienced physician to achieve in most instances a proper cardiac evaluation by other means should restrict the use of catheterization of the left heart to those cases in which other studies have failed to provide a satisfactory diagnosis.

BENIGN LOCALIZED PLEURAL MESOTHELIOMA

Mesothelioma of the pleura is almost always described as generalized and malignant. The exceedingly rare occurrence of localized benign mesothelioma prompted the report of two cases by Heaney *et al.* (*J. Thoracic Surg.*, 34: 553, 1957). Both patients had migratory joint symptoms on admission and their pulmonary lesions were discovered only on routine chest roentgenograms. Thoracotomy with local excision of the tumour in both cases led to rapid disappearance of the extrathoracic symptoms. The characteristic gross and histologic appearance of a localized benign tumour composed of fibrous tissue cells was demonstrated in each instance. The satisfactory prognosis of this localized, benign form of pleural tumour is emphasized.

COURSE IN CIVIL DEFENCE

The Canadian Civil Defence College will be running another course for physicians and dentists at the College in Arnprior, Ontario, from March 3-7 (inc.), 1958. These courses are offered free to the medical profession twice a year and are designed to familiarize Canadian doctors with the most efficient measures in coping with any civil disaster in general and more particularly with ABC warfare (atomic, bacterial and chemical). Experience has proved in the past that goodwill in emergency

states accomplishes considerably more when backed by planning and training than otherwise. In the event of warfare the prognosis is obviously guarded but if chances of survival are limited would it not be all the wiser to make the most of them? The course consists mostly of lectures given by Canadian authorities on the matter. A few demonstrations are also included. The program is well organized, the quarters are comfortable and the catering excellent. Physicians who are interested should communicate with their local Civil Defence Coordinator for further information.

15TH BRITISH CONGRESS OF OBSTETRICS AND GYNÆCOLOGY

The Fifteenth British Congress of Obstetrics and Gynæcology will be held in Cardiff on July 14, 15 and 16, 1959. These dates have been chosen with the convenience of Canadians going to the C.M.A.-B.M.A. meeting in Edinburgh in mind.

The program will include a symposium on the influence of certain factors in pregnancy and labour on the future development of the child. Amongst other subjects proposed for discussion are psychosomatic gynæcology, ovarian malignant disease, œstrogen metabolism, and the place of oxytocic drugs in obstetrics. All communications relating to this congress should be addressed to the Honorary Secretaries, British Congress, Maternity Hospital, Glossop Terrace, Cardiff, Wales.

THE AMERICAN COLLEGE OF SURGEONS

The American College of Surgeons announces a four-day meeting for surgeons and nurses in New York City, March 3-6, 1958. The headquarters hotels will be the Waldorf-Astoria, Commodore, Biltmore and Belmont-Plaza. The program will include hospital clinics, panel discussions, symposia, scientific papers, technical exhibits, medical motion pictures, ciné-clinics, general sessions and special programs in otolaryngology, ophthalmology, urology, gynæcology and obstetrics, orthopædic surgery and thoracic surgery. A program of joint interest to surgeons and nurses will include discussions on current problems in nursing care, from nursing of cardiac patients to psychological resources for surgical patients. Various New York hospitals will be visited, and home care programs also demonstrated. A new feature will be the Fellowship Luncheon, with a panel discussion on College affairs; the aim will be to promote better understanding of the College and its objectives. Information from Dr. H. P. Saunders, 40 East Erie Street, Chicago 11, Illinois.

AMERICAN ORTHOPSYCHIATRIC ASSOCIATION

The American Orthopsychiatric Association announces its 36th Annual Meeting for March 6, 7 and 8 at the Hotels Commodore and Roosevelt, New York City.

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The program will include a session on community mental health services, arranged jointly with the American Public Health Association, and joint sessions with the American Academy of Child Psychiatry and the American Association of Psychiatric Clinics for Children. The President, Dr. Reginald S. Lourie, will address the opening session on Thursday morning, March 6. A symposium on the future of psychoanalysis in relation to advances in biochemistry is scheduled for March 7. Other topics for discussion include clinical studies of murder, approaches to delinquency, the problem of creativity, adolescent schizophrenia, problem families, training of psychotherapists, anorexia nervosa, community services for children, the use of newer drugs in child psychiatry, college guidance, diagnosis of brain damage, mental health epidemiology and factors associated with mental disorders in the aged. Further information from Dr. Marion F. Langer, Executive Secretary, American Orthopsychiatric Association, 1790 Broadway, New York 19, N.Y.

NEEDLE BIOPSY OF THE PARIETAL PLEURA IN TUBERCULOSIS

Vim-Silverman needle biopsy of the parietal pleura in 22 cases of pleural effusion treated as tuberculous yielded tissue with caseating tubercles in 12 cases. This procedure was the single most rewarding diagnostic tool in this series. When biopsy was used in conjunction with other diagnostic methods, a diagnosis of tuberculosis could be established in approximately three-fourths of the patients. Needle biopsy has the advantages of simplicity, convenience, innocuousness, and repeatability.—W. Weiss, *Am. J. M. Sc.*, 234: 431, 1957.

POSTGRADUATE COURSE ON DISEASES OF THE CHEST

The Council on Postgraduate Medical Education of the American College of Chest Physicians will sponsor the 11th Annual Postgraduate Course on Diseases of the Chest at the Warwick Hotel, Philadelphia, March 3-7, 1958. The most recent advances in the diagnosis and treatment of chest diseases—medical and surgical—will be presented. The tuition fee is $75, including round-table luncheons.

Further information from the Executive Director, American College of Chest Physicians, 112 East Chestnut Street, Chicago 11, Illinois.

HEALTH LEAGUE OF CANADA

The 37th Annual Meeting of the Health League of Canada will take place at the Royal York Hotel in Toronto on February 13, 14 and 15, 1958. During this three-day conference, the following health topics will be discussed: multiple sclerosis, epilepsy, diabetes, relationship of the medical profession to voluntary health associations,

the church and health, preventive aspects of problems of health in infants and children, the integration of prevention in the practice of general medicine, hospital insurance, industrial health, gerontology and mental health.

Dr. A. D. Kelly, General Secretary of the Canadian Medical Association, will be the guest speaker at the luncheon meeting of February 13. The topic of his talk will be: "Relationship of the Medical Profession to Voluntary Health Organizations". In similar circumstances the next day, Dr. Wilson G. Smillie, world authority on preventive medicine and public health, will address the meeting on "The Integration of Prevention in the Practice of General Medicine". "The Significance of Industrial Medicine" will be discussed by Dr. Robert Collier Page, Consultant in Manpower Development, on Saturday, February 15.

A detailed program will be forwarded on request by the Health League of Canada, 111 Avenue Road, Toronto, Ontario.

NATIONAL HEALTH WEEK FEBRUARY 2-8, 1958

Canadians from coast to coast will be observing National Health Week, which commences February 2. Sponsored by the Health League of Canada, this event presents an opportunity to promote public interest in all phases of health education. Then too, National Health Week is an opportune time for doctors to convey to their patients that "Good health is a golden key to better living—but we must all accept the responsibility of working for it."

SOCIETY OF OBSTETRICIANS AND GYNÆCOLOGISTS OF CANADA

The Society of Obstetricians and Gynæcologists of Canada offers the sum of $1000 to any Canadian doctor for his or her original contribution to scientific information in the field of human reproduction. Any candidate wishing to qualify for this award should forward his paper to Dr. F. P. McInnis, Secretary, Society of Obstetricians and Gynæcologists of Canada, 1230 Avenue Road, Toronto, Ont., before March 15, 1958.

THALLIUM POISONING

The Council on Drugs of the American Medical Association has once more drawn attention to the insidious effects of thallium compounds, which are not uncommonly used as poisons for rats, mice and cockroaches. In the past two years there has been an alarming growth in numbers of cases of thallium poisoning in Texas; usually the history is that a child eats bait which was set down for household pests. The usual form of poison is thallium sulphate, which resembles table salt in general appearance and is readily absorbed through the skin and from the alimentary tract. The thallium ion is extremely toxic, and symptoms of acute poisoning resemble those due to other heavy metals. They develop slowly with digestive disturbances

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including a metallic taste, salivation, stomatitis, nausea, vomiting and abdominal pain. Vasomotor disturbances may lead to puffiness of cheeks, eyelids and lips. Tingling and pain in the hands and feet, muscle weakness, delirium, convulsions and coma may ensue and death may follow within a few days or be delayed for several weeks. Recovery takes place over a period of months, and residual nervous disorders are not uncommon. Symptoms of chronic poisoning are similar but milder. Loss of hair is a common sign in chronic cases. Little is known about the specific treatment of thallium poisoning, of which over 63 cases have occurred in small children in Texas within six months. Similar cases have been reported in many other states. The Council on Drugs suggests that thallium salts should not be used as household chemicals. Reprints of the entire report may be obtained by writing to the Committee on Pesticides, American Medical Association, 535 North Dearborn Street, Chicago 10, Ill., U.S.A.

HEARING IN CHILDREN

The American Academy of Ophthalmology and Otolaryngology, through its Subcommittee on Hearing in Children of the Committee on Conservation of Hearing, has been conducting a long-term nation-wide study of problems relating to the conservation of hearing in children. The specific aims are to develop the most efficient case-finding methods and use these in estimating the magnitude of the problem; to study state laws and review current practices and facilities for rehabilitation; to help develop rehabilitation standards; and ultimately to use the findings in assisting professional workers to improve and enhance programs in hearing loss.

A full-time executive director, Dr. Eldon L. Eagles, has been engaged, with offices at the Graduate School of Public Health, University of Pittsburgh, Pittsburgh 13, Pa. An initial study is being conducted in Pittsburgh to identify early medical signs and symptoms which may indicate danger of hearing impairment, to measure the psychological, social and other effects of such impairment and to develop efficient and economical methods for the testing of hearing in children.

The Canadian member of the Subcommittee on Hearing in Children is Dr. Hollie E. McHugh, Montreal.

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WORLD CONGRESS OF GYNÆCOLOGY AND OBSTETRICS

The Second World Congress of the International Federation of Gynæcology and Obstetrics will take place in the new Queen Elizabeth Hotel, Montreal, June 22-28, 1958. Round table conferences will be held in gynæcology and in obstetrics. The subjects are as follows:

Gynæcology: Limits of pelvic surgery in the treatment of carcinoma of the cervix; correlation of psychosomatic medicine in the ovarian function; diagnosis of carcinoma of the cervix; genital tuberculosis.

Obstetrics: Psycho-prophylactic preparation for labour; physiology and pathology of the contraction of the human gravid uterus; anæmia of pregnancy; toxæmias of pregnancy.

All correspondence should be addressed to the Montreal Committee, Second World Congress, International Federation of Gynæcology and Obstetrics, 1414 Drummond St., Suite 220, Montreal 25, Quebec.

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SCOTTISH PRIZE IN RADIOLOGY

A David Anderson-Berry silver-gilt medal, together with a sum of money amounting to not less than £100, will be awarded in 1958 by the Council of the Royal Society of Edinburgh. The prize will be awarded for recent work on the effects of x-rays and other forms of radiation on living tissues. Published work will be taken into consideration if submitted to the Society with the application. In addition to direct application for the prize, proposals may be made on behalf of others.

Applications and proposals must be in the hands of the General Secretary, Royal Society of Edinburgh, 22-24 George Street, Edinburgh 2, Scotland, **not later than March 31, 1958.**

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COMMONWEALTH MEDICAL ADVISORY BUREAU

Canadians who have visited the British Medical Association in London and had the benefit of advice from the Commonwealth Medical Advisory Bureau there will no doubt wish the retiring Medical Director, Brigadier H. A. Sandiford, a pleasant retirement. Brigadier Sandiford has left the Bureau, and the Directorship was taken over by R. A. Pallister, O.B.E., M.D., M.R.C.P., D.T.M. & H., on January 1.

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AMERICAN BOARD OF OBSTETRICS AND GYNÆCOLOGY

The next scheduled examinations (Part II), oral and clinical for all candidates will be conducted at the Edgewater Beach Hotel, Chicago, Illinois, by the entire Board from May 7 to May 17, 1958. Formal notice of the exact time of each candidate's examination will be sent him in advance of the examination dates.

Candidates who participated in the Part I examinations will be notified of their eligibility for the Part II examinations as soon as possible.

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POSTGRADUATE COURSE IN TRAUMA

The second annual postgraduate course in fractures and other trauma will be given by the Chicago Committee on Trauma of the American College of Surgeons from Wednesday, April 16, to Saturday, April 19, at the John B. Murphy Memorial Auditorium, 40 East Erie St., Chicago, Ill. All phases of trauma will be discussed. Topics will include trauma of the hand, head, chest, abdomen, heart, knee and shoulder, treatment of burns, athletic injuries, and other subjects selected in answer to a questionnaire sent last year's registrants. Illustrated lectures, patient demonstrations, and question-and-answer periods will also be held. The registration fee is $50. Residents, interns and students will be admitted free if a note of identification from chief of service or dean is provided. Further in-

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formation from Dr. John J. Fahey, 1791 W. Howard St., Chicago 26, Ill.

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BAHAMAS MEDICAL CONFERENCE

The fifth Bahamas Medical Conference will be held at the Dolphin Hotel in Nassau, April 1-12, 1958. For participants in the conference and their families the Dolphin Hotel will charge reduced rates: $14.00 per person per day, two in one room; $18.00 per person per day, one in one room; including breakfast and dinner. Accommodation at the new Dolphin is limited. Additional rooms have been reserved at the nearby British Colonial Hotel at $20.00 per person per day, two in one room; $30.00 per person per day, one in one room; including breakfast and dinner. All reservations for either hotel should be made by writing directly to the Manager, Dolphin Hotel, Nassau, Bahamas (air mail requires a ten-cent stamp).

The meetings will be held at the top floor of the Dolphin Hotel, 9:30-11 a.m. and 6-7:30 p.m. The usual certificate of attendance will be issued.

The sixth Bahamas Medical Conference will be held December 1-15, 1958.

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PINEAL EXTRACT IN SCHIZOPHRENIA

For the last six years Altschule of Boston, Mass., has been interested in the use of pineal gland extract in the treatment of chronic schizophrenia. He has recently reported (*New England J. Med.*, 257: 919, 1957) on the use of beef pineal extract in eight schizophrenic patients, who received 1 g. of the powdered extract by injection daily. Clinical improvement appeared usually within a week of the onset of treatment, and lasted from a few days to a few weeks. This was accompanied by a rise in blood glutathione and eosinophils in some patients. In one group receiving the extract, a state of refractoriness was observed within a few weeks which cleared up in a month or two if treatment was stopped in less than three weeks but which lasted indefinitely if it was overlooked and treatment continued for a month. Administration of hydrocortisone nullified the effect of the pineal extract in two cases, but the expected action was obtained as soon as the hydrocortisone was stopped. When a protein-free extract was produced, the same clinical improvement and rise in blood glutathione were obtained, but refractoriness was not observed even after four 8-10 day courses. Tryptic digestion of the extract brought about only a slight reduction in potency. According to the author the active substance may be a peptide with a molecular weight of approximately 1000. Standardizing the potency of extracts poses a problem which has not yet been completely solved. Considering the low potency of material obtained by acid extraction and the negligible reduction in potency resulting from the action of trypsine, the author suggests the possibility of administering pineal extract in the form of enteric-coated tablets.

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TRAFFIC ACCIDENTS IN FRANCE

At a recent meeting of the French *Académie nationale de médecine*, Mr. X. Leclainche expressed his concern about the growing number of car accidents in his country. He reminded the assembly that Dr. Pierre Devraigne had previously reported on motorcycle accidents, and had suggested the mandatory use of crash helmets for drivers and passengers. Mr. Leclainche pointed out that driving permits seemed to be granted in complete disregard of the health and age of the applicants. Everyone knew of physically or mentally impaired drivers who had nevertheless obtained a permit and who did not have to renew it for the rest of their lives. The reporter was worried by the ever increasing power and speed of standard assembly line models of motor cars. He suggested that the following measures could contribute in halting the trend towards more accidents and fatalities: (1) A sharp increase in the strictness of the driving tests with the issuing at first of a temporary permit only, valid for several months and not followed by a permanent one until the applicant had shown his capabilities. (2) Special permits for the owners of high-powered cars; these would be based on stiffer tests depending on the speed and accuracy of the nervous reflexes. Tests could be made difficult in proportion to the speed of the car driven. (There is no speed limit on the highways in France outside of towns and villages).* (3) Driving licences should be granted only on presentation of a certificate of physical aptitude based on a strict medical examination. (4) A time limit should be imposed on driving licences, instead of making them valid for life. At expiration date, driving and aptitude tests could be renewed if warranted. A member of the assembly, Mr. Bourguignon, suggested measurement of vestibular chronaxia as a means of detecting slight cerebral and autonomic nervous imbalance in driving applicants. — *Bulletin de l'Académie nationale de médecine*, meeting of October 15, 1957.

*The application of a speed limit of 75 kilometres per hour in Belgium reduced highway accidents by 50%.